Neurodevelopmental Problems in a Clinical Sample of Children with Anxiety Disorders

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Abbreviations

ADHD	Attention deficit/hyperactivity disorder
CCC-2	Children's communication checklist
DCD	Developmental coordination disorder
DSM	Diagnostic and statistical manual of mental disorders
GAD	Generalized anxiety disorder
GCC	General communication composite
ICD	International classification of diseases
Kiddie-SADS P/L	Schedule for affective disorders and schizophrenia for school-aged children (6-18 years): Present and lifetime version
M-ABC	Motor assessment battery for children
MASC-10	The multidimensional anxiety scale for children, short version
OCD	Obsessive compulsive disorder
PTSD	Posttraumatic stress disorder
RBUP	Centre for child and adolescent mental health, eastern and southern Norway
REK	Regional committee for medical and health research ethics
SCT	Sluggish cognitive tempo
SIDC	Social interaction deviance composite
SSRS	Social skills rating system
WASI	Wechsler abbreviated scale of intelligence

List of papers

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Abstract

Anxiety disorders are among the most common psychiatric conditions in childhood and adolescence, and may persist into adulthood. The development of anxiety disorders seems to be caused by a complex interaction between genetic and environmental factors. Children with neurodevelopmental disorders, such as specific language impairment and developmental coordination disorder, have been shown to exhibit an increased prevalence of anxiety disorders. However, the literature on neurodevelopmental disorders in children with anxiety disorders is sparse, rendering it unresolved whether the presence of neurodevelopmental disorders constitute an important problem among children with anxiety disorders.

Objectives:

The main objective of this thesis was to investigate the association between anxiety disorders and neurodevelopmental delays/disorders in children studied within a clinical setting. The more specific aims of investigation were:

- To compare the frequency and degree of motor impairment in a clinical sample of children with anxiety disorders, ADHD, and comorbid anxiety disorders and ADHD, compared with non-referred controls (paper I).
- To compare the frequency and degree of language impairment in a clinical sample of children with anxiety disorders, ADHD, and comorbid anxiety disorders and ADHD, compared with non-referred controls (paper II).
- To evaluate how anxiety symptoms, ADHD symptoms, and language ability predict social skills in a clinical sample of children with anxiety disorders with and without comorbid ADHD (paper II).
- To investigate the relationship between anxiety disorders, ADHD, and sluggish cognitive tempo (SCT) in a clinical sample of children with anxiety disorders, ADHD, and comorbid anxiety disorders and ADHD, compared with non-referred controls (paper III).
- To explore the association between SCT and some selected neurocognitive measures in a clinical sample of children with ADHD with and without comorbid anxiety disorders (paper III).

Material and methods:

All three studies included in this thesis are based on the same sample. The sample consisted of a total of 141 children (90 males, 51 females) aged 7-13 years. The children were assigned to the following four groups: Referred children with anxiety disorders (n = 41), ADHD (n = 39), comorbid anxiety disorders and ADHD (n = 25), and controls (n = 36). The clinical children were recruited from referrals to two Norwegian outpatient child and adolescent psychiatric clinics over a 17-month period (autumn 2007 to spring 2009). Diagnoses were established using the Schedule for Affective Disorders and Schizophrenia for School-Aged children (6-18 years): Present and Lifetime Version (Kiddie-SADS P/L). Motor performance was assessed using the Motor Assessment Battery for Children (M-ABC) (paper I). Language skills were investigated with the verbal subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) and the Children's Communication Checklist (CCC-2) (paper II). Social skills were measured with the Social Skills Rating System (SSRS) (paper II). SCT was assessed by the SCT-17 questionnaire (paper III). Neurocognitive measures of reaction time, verbal memory, and spatial memory were obtained by testing the child (paper III).

Results:

We found that neurodevelopmental disorders, as conceptualized by motor and language impairment, were frequent among children with anxiety disorders. A total of 46 % of the children in the anxiety disorders group, and 36 % of the comorbid anxiety disorders and ADHD group exhibited motor impairment. Regarding language skills, 50 % of the children in the anxiety disorders group and 76 % of the children in the comorbid anxiety disorders and ADHD group exhibited scores consistent with language impairment. Taken together, neurodevelopmental disorders were found in 63 % of the children in the anxiety disorders group and 88 % in the comorbid anxiety disorders and ADHD group.

In addition, we found an elevated level of sluggish cognitive tempo among children with comorbid anxiety disorder and ADHD compared with children who had ADHD without comorbid anxiety disorder.

Conclusions:

The three articles included in this thesis examine different areas of neurodevelopmental difficulties in referred children with anxiety disorders, compared with children with ADHD, children with comorbid anxiety disorders and ADHD, and non-referred controls.

The main findings are that referred children with anxiety disorders exhibit a high prevalence of neurodevelopmental disorders (as conceptualized by significant motor or language impairment), and that referred children with comorbid anxiety disorders and ADHD exhibit a higher level of SCT than children with ADHD alone. The present findings underscore the importance of routinely assessing neurodevelopmental disorders in children with anxiety disorders. Furthermore, the findings provide a new perspective on the controversy regarding the utility and impact of SCT, by demonstrating that children with comorbid anxiety disorders and ADHD exhibit more SCT symptoms than children with 'pure' ADHD, regardless of subtype of ADHD or degree of hyperactivity/impulsivity symptoms.

1 Introduction

Anxiety disorders are among the most common psychiatric conditions in childhood and adolescence, with lifetime estimates in the community ranging from 8.3 – 27.0% (Costello, Egger, & Angold, 2005), with the highest estimates found in the oldest samples. Childhood anxiety disorders may persist into adulthood, causing significant suffering for the affected children and their families (Goodwin, Fergusson, & Horwood, 2004).The specific anxiety disorders include separation anxiety disorder, generalized anxiety disorder (GAD), specific phobia, social phobia, posttraumatic stress disorder (PTSD), obsessive compulsive disorder (OCD), and panic disorder with or without agoraphobia (American Psychiatric Association, 2000). The age of onset differs between the anxiety disorders, with separation anxiety disorder and specific phobias typically presenting before the age of 12; OCD and social phobia typically presenting in late childhood and throughout adolescence; and panic disorder, agoraphobia, and GAD typically presenting in adolescence (Beesdo, Knappe, & Pine, 2009; Heyman et al., 2003). Childhood and adolescence taken together, GAD is the most common anxiety disorder and panic disorder the least common (Costello, et al., 2005).

The development of anxiety disorders seems to be caused by a complex interaction between genetic and environmental factors (Gregory & Eley, 2007), and heritability figures are reported to be about 30-40 % (Hettema, Neale, & Kendler, 2001). Research has focused on both possible internal vulnerability factors, including temperament, cognitive, and neurobiological factors, and possible external vulnerability factors including parenting style, parent/child interaction, and life events (Manassis, Hudson, Webb, & Albano, 2004; Rapee, Schniering, & Hudson, 2009).

1.1 Clinical background for the study

Before conducting this study, I had been working for some years with neuropsychiatric assessment of children referred to a child and adolescent mental health clinic. The indication for conducting such assessment was that one suspected that developmental difficulties played a part in the child's impairment. During this period it struck me that while externalizing problems like hyperactivity were often seen as indicating a need for neuropsychiatric assessment, this was not the case for internalizing/emotional problems. My impression was that children with emotional disorders had to exhibit rather obvious signs of

neurodevelopmental difficulties before this was seen as relevant and a neuropsychiatric assessment was requested. When an anxious child withdrew from physical play or from conversations in the schoolyard, this was often interpreted as a lack of interest in play activities, or that the child did not want to or did not dare to participate. However, my clinical impression was that many children with anxiety had problems with motor ability or language ability, making it difficult for them to participate. This implied that, in addition to "will not" and "dare not", there was also an element of "can not".

Describing this as my own individual enlightenment process is not honest. From the day I started working at Nic Waal's Institute in 2001, and for the next couple of years, I received clinical supervision from Dr. med. Hanne Kristensen. She had just submitted her doctoral thesis on children with selective mutism, a disorder closely related to social phobia. In her work she found a high prevalence of developmental disorder/delay in children with selective mutism. Subsequently, she did not ease my growing feeling that developmental difficulties were frequently overlooked in children with anxiety disorders. The clinical supervision ended when Hanne started her post doctoral research and reduced her employment at Nic Waal's Institute. However, she continued to encourage my concern and, wanting to extend her recent findings of neurodevelopmental difficulties in a population-based sample of children with social phobia, ended up inviting me to discuss the possibility of conducting a clinical study. A literature search revealed that research addressing neurodevelopmental disorder/delay in referred children with anxiety disorders was sparse. Hence, we started to plan the clinical study which the present thesis is a result of.

1.2 Anxiety disorders and the comorbidity with ADHD

There is a high degree of comorbidity between anxiety disorders and attention deficit/hyperactivity disorder (ADHD), with an odds ratio of 3.0 (95% CI: 2.1-4.3) found in studies of ADHD in anxiety disorders (Costello, et al., 2005) and a prevalence of approximately 25% found in studies of anxiety disorders in ADHD (Schatz & Rostain, 2006). The comorbidity has not been shown to affect treatment outcome in the treatment of anxiety disorders, but when it comes to treatment of ADHD the findings are more ambiguous, with some findings indicating that comorbid anxiety disorders predict a poorer outcome of the ADHD treatment (Ollendick, Jarrett, Grills-Taquechel, Hovey, & Wolff, 2008).

In studies of neurodevelopmental delays/disorders in children with anxiety, the comorbidity with ADHD is especially important to account for, because the relationship between ADHD and neuropsychological impairment is well established (Nigg, 2005). The increased prevalence of motor impairment in children with ADHD has attracted attention for decades (Fliers et al., 2008; Gillberg, Carlstrom, & Rasmussen, 1983), and for a period this was especially reflected here in Scandinavia where the concept "disorder of attention, motor control and perception" (DAMP) was used to describe this group of children (Gillberg, 2003). Furthermore, studies have revealed a high prevalence of language impairment in children with ADHD (Bruce, Thernlund, & Nettelbladt, 2006; Tirosh & Cohen, 1998). Thus, when studying neurodevelopmental delays/disorders in children with anxiety disorders it is important to evaluate whether the findings are attributable to comorbid ADHD.

1.3 Anxiety disorders and neurodevelopmental delays/disorders

Neurodevelopmental deficits have been defined in several different ways and with varying nomenclature (e.g. soft/ subtle/ minor/ equivocal neurological signs) (Pine, Wasserman, Fried, Parides, & Shaffer, 1997; Shaffer, 1978; Touwen, 1979; Vance et al., 2006). Motor abnormalities are consistently included in the definitions, and some also include language impairment. Assessment of neurodevelopmental deficits in children with mental health problems in general has the potential to bring knowledge of biological risk factors and of possible correlates in the central nervous system. However, this has been hampered by the fact that many of the signs looked for have been composite functions, taken from many different functional areas, rendering it unclear whether they result from specific or diffuse brain abnormalities (Dazzan & Murray, 2002). An increased level of neurodevelopmental deficits has been found in a wide range of psychiatric and developmental conditions, e.g., anxiety disorders, ADHD, bipolar disorder, post traumatic stress disorder, dyslexia, mental retardation, pervasive developmental disorders, personality disorders, and psychotic disorders (Brookes & Stirling, 2005; Chan, Xu, Heinrichs, Yu, & Wang, 2010; De la Fuente et al., 2006; Gurvits et al., 2000; Gustafsson et al., 2010; Lindberg et al., 2004; Mayoral et al., 2010; Negash et al., 2004; Shaffer et al., 1985). It is not clearly established whether neurodevelopmental deficits are more related to some psychiatric disorders than to others. Together with the lack of clear implications for function, prognosis, or treatment, this makes

it difficult to evaluate the clinical implications of the presence of neurological deficits. In other words, the presence of neurodevelopmental problems would be easier to interpret if they represented more clearly defined functions and had a clearer implication for daily function and/or treatment.

During the compilation of DSM-V and ICD-11 it has been suggested to group some disorders together as 'neurodevelopmental disorders' (Andrews, Pine, Hobbs, Anderson, & Sunderland, 2009). These are disorders characterized by a 'delay/deviance in maturationally influenced psychological features' (Rutter, Kim-Cohen, & Maughan, 2006), and include motor and communication disorders, such as developmental coordination disorder and specific language impairment. ADHD has been suggested to be grouped together with the neurodevelopmental disorders (Rutter, et al., 2006), but will probably be allocated to the 'externalizing cluster' (Andrews, et al., 2009). Taken together, when investigating neurodevelopmental problems in children with anxiety disorders it would be appropriate to investigate the anxiety disorders' relationship with neurodevelopmental disorders or clearly defined neuropsychological impairment, rather than with the more ambiguous neurodevelopmental deficits/ soft signs.

1.3.1 Anxiety disorders and motor impairment

Motor impairment may occur with varying degrees of severity, from slight clumsiness to developmental coordination disorder (DCD). The main DSM-IV criterion for DCD is: 'Performance in daily activities that require motor coordination is substantially below that expected given the person's chronological age and measured intelligence' (American Psychiatric Association, 2000). DCD represents a challenge for the affected child in a multitude of daily activities both at home and at school (Summers, Larkin, & Dewey, 2008; Wang, Tseng, Wilson, & Hu, 2009). An increased prevalence of internalizing problems/ anxiety disorders has been found in samples of children with DCD (Dewey, Kaplan, Crawford, & Wilson, 2002; Pratt & Hill, 2011; Schoemaker & Kalverboer, 1994; Skinner & Piek, 2001). Furthermore, there are studies suggesting that motor coordination problems are predictive of the later development of anxiety disorders (Piek, Barrett, Smith, Rigoli, & Gasson, 2010; Shaffer, et al., 1985; Sigurdsson, van Os, & Fombonne, 2002).

Despite this, motor impairment in children with anxiety disorders has attracted little attention in research. The authors of a recent review found only two clinical studies between

1997 and 2007 that met their inclusion criteria of more than 30 participants, emotional problems or psychiatric disorders assessed by standardized diagnostic instruments, and measurement of gross motor performance of verifiable psychometric quality (Emck, Bosscher, Beek, & Doreleijers, 2009). The first of the clinical studies included 102 inpatient children aged 5-13 years (Baumann, Loffler, Curic, Schmid, & von Aster, 2004). The children were divided into four subgroups including externalizing disorder, internalizing disorder, combined internalizing and externalizing disorder, and other disorders. All groups exhibited motor coordination below the average according to a norm-referenced German motor coordination test. However, the study has some important limitations. Firstly, the allocation of children into subgroups was based on diagnostic information from the children's psychiatric records, not from standardized diagnostic assessment. Secondly, the paper includes no information on the children's level of intelligence quotient (IQ), even though a majority of the included children were reported to be attending special schools. Finally, the study did not include a control group. In the second clinical study the researchers used a standardized test to assess neurological subtle signs in 99 outpatient children aged 6-12 years and a control group of 20 healthy children (Vance, et al., 2006). Based on a semi-structured diagnostic interview the outpatient children were assigned to the three diagnostic groups ADHD combined type (ADHD-C), dysthymic disorder, and anxiety disorder. All children attended ordinary primary schools and exhibited IQ scores above 70. The authors found that children with anxiety disorders exhibited more neurological subtle signs, particularly mirror movements, than controls, but fewer than children with ADHD-C. A limitation to this study is that the ambiguity of neurological subtle signs makes it difficult to evaluate the clinical implications of the findings. To my knowledge there are no clinical studies of motor impairment in children with anxiety disorders published after the period included in the aforementioned review.

Two population-based studies have assessed motor performance in children with anxiety disorders. The first study included 150 children, aged 11-12 years, assigned to the five diagnostic groups social anxiety disorder, ADHD, social anxiety disorder and ADHD, other disorder, and no disorder (Kristensen & Torgersen, 2008). Diagnoses were based on a semi-structured diagnostic interview and motor function was assessed with the Movement Assessment Battery for Children (M-ABC). The authors found that children with social anxiety disorder and/or ADHD exhibited poorer motor scores than children with no disorder. The second study included 27 children with anxiety disorder and 27 controls, all aged 8-11 years (Ekornås, Lundervold, Tjus, & Heimann, 2010). Diagnoses were based on a

semi-structured diagnostic interview and motor function was assessed with the M-ABC. The authors found that children with anxiety disorders exhibited poorer motor scores than controls.

In addition to the aforementioned studies a smaller clinical study of 20 children with anxiety disorders and 20 controls, aged 7-14 years, found children with anxiety disorders to exhibit more balance problems than controls (Erez, Gordon, Sever, Sadeh, & Mintz, 2004). However, more than half of the children with anxiety disorders in this study had a comorbid ADHD, which may represent a serious bias given the relationship between ADHD and motor impairment. This study of balance problems in children with anxiety disorders is, together with a review of the co-occurrence of anxiety and balance dysfunction in adults (Balaban & Jacob, 2001), regularly interpreted as indicating a specific association between balance problems and anxiety (Cairney, Veldhuizen, & Szatmari, 2010; Emck, et al., 2009; Kogan, Lidor, Bart, Bar-Haim, & Mintz, 2008). However, caution is needed because these assumptions rely on the finding of balance problems, without assessing other motor problems. To conclude that there is a specific association, one would need to substantiate that anxiety is related stronger to balance problems than to other motor problems.

Taken together, two population-based studies found impaired motor ability among children with anxiety disorders. However, there is a lack of clinical studies on motor impairment in children with anxiety disorders. In future studies it would be advisable to apply well known, standardized, and comprehensive assessment of psychiatric diagnoses and motor function, and include assessment of IQ.

1.3.2 Anxiety disorders and language impairment

'Specific language impairment' is often used as a term describing the 'Communication disorders' as defined in DSM-IV (American Psychiatric Association, 2000, section 315.3x) and the 'Specific developmental disorders of language' as defined in ICD-10 (World Health Organization, 1993, section F80.x). The term 'specific' implies that the child's language ability is significantly below his or her non-verbal intellectual capacity. Specific language impairment, where the principal problem is with language structure, is also used as opposed to 'pragmatic language impairment', where the child exhibits problems in their ability to use and understand social and contextual clues in communication (Bishop & Baird, 2001).

An increased prevalence of anxiety disorders has been found in children and adolescents with specific language impairment (Beitchman, Nair, Clegg, Ferguson, & Patel, 1986; Conti-Ramsden & Botting, 2008), and specific language impairment in early childhood has been found to be predictive of anxiety disorders in early adulthood (Beitchman et al., 2001).

Although there is a growing literature on the relationship between language and shyness (Coplan & Evans, 2009), which is a temperamental concept closely related to anxiety disorders in general and social phobia in particular (Coplan & Weeks, 2009), the language abilities of children with social phobia and other anxiety disorders have attracted little attention in research. Diagnostically diverse clinical populations have been shown to exhibit a prevalence of specific language impairment of more than 50% (Cohen, Davine, Horodezky, Lipsett, & Isaacson, 1993; Giddan, Milling, & Campbell, 1996). A cross-sectional population-based study found that children with social phobia exhibited poorer verbal IQ scores than controls (Kristensen & Torgersen, 2008), and a clinical study found that children with anxiety disorders showed some degree of pragmatic language problems (Pine, Guyer, Goldwin, Towbin, & Leibenluft, 2008). However, to my knowledge, no study has examined specific language impairment in referred children with anxiety disorders. Several studies have demonstrated that there is a link between language and social skills (Durkin & Conti-Ramsden, 2007; Hart, Fujiki, Brinton, & Hart, 2004; Hebert-Myers, Guttentag, Swank, Smith, & Landry, 2006). Social skills are of great importance in many aspects of the daily lives of children, e.g. when interacting with peers, teachers, and family. These skills may be especially important in children with anxiety disorders, as children with anxiety disorders and poor social skills have been found to be particularly vulnerable to peer victimization (Crawford & Manassis, 2011). To my knowledge, there are no studies examining the relationship between social skills and language impairment in childhood anxiety disorders.

1.3.3 Anxiety disorders and attentional problems

ADHD is in recent literature described as ‘essentially a complex disorder in unfolding development of the unconscious self-management system of the brain’ (Brown, 2009), and arguments have been put forward to group ADHD within the neurodevelopmental cluster in the forthcoming diagnostic categorizations (Rutter, et al., 2006).

As mentioned in section 1.2, children with anxiety disorders exhibit an increased prevalence of ADHD and vice versa. In older studies, using DSM-III criteria (American Psychiatric Association, 1980), anxiety was found to be more prevalent in children with attention deficit disorder without hyperactivity (ADD/Wo) than in children with attention deficit disorder with hyperactivity (Lahey, Schaughency, Hynd, & Carlson, 1987). However, more recent studies, using DSM-IV criteria (American Psychiatric Association, 2000), have found anxiety to be equally distributed across ADHD subtypes (Elia et al., 2009; Mayes, Calhoun, Chase, Mink, & Stagg, 2009; Power, Costigan, Eiraldi, & Leff, 2004).

An important change in ADHD criteria in the transition from DSM-III to DSM-IV was the rejection of the inattentive symptoms 'daydreams' and 'sluggish/drowsy' (Frick, Lahey, Applegate, & Kerdyck, 1994). A subsequent study, addressing whether this change would lead to the omission of a subtype of ADHD, found that the two discarded symptoms, together with the symptom 'forgetful', formed a distinct factor (McBurnett, Pfiffner, & Frick, 2001). The authors suggested that this factor identifies a subtype of ADHD/inattentive type (ADHD/I) that is characterized by sluggish cognitive tempo (SCT). SCT has later come to be described by distinct attentional symptoms that include 'sluggish/slow to respond', 'seems to be in a fog', 'drowsy or sleepy', 'easily confused', and 'daydreams/ stares into space' (Hartman, Willcutt, Rhee, & Pennington, 2004). The results from research on SCT have been ambiguous, with some findings supporting the existence of an SCT subtype (Carlson & Mann, 2002; Garner, Marceaux, Mrug, Patterson, & Hodgens, 2010; Hartman, et al., 2004), while other findings question the existence or clinical importance of such a subtype (Harrington & Waldman, 2010; Hinshaw, Carte, Fan, Jassy, & Owens, 2007; Todd, Rasmussen, Wood, Levy, & Hay, 2004). Interestingly, studies that identified an SCT subgroup of ADHD/I, i.e. rendering it more similar to the DSM-III-based ADD/Wo, found that this group exhibited more anxiety compared with children with ADHD without SCT. More research has been called for to explore the relationship between SCT, ADHD, anxiety disorders, and neurocognitive measures (Nigg, 2005; Schatz & Rostain, 2006). To my knowledge, no studies have compared SCT between children with anxiety disorders, ADHD, both conditions, and neither condition.

There are few studies relating SCT to neurocognitive measures. A study that followed girls with ADHD prospectively into adolescence, did not find that a refined ADHD/I group with high levels of SCT differed in neuropsychological functioning from other girls with ADHD/I or ADHD/combined type (ADHD/C) (Hinshaw, et al., 2007;

Hinshaw, Carte, Sami, Treuting, & Zupan, 2002). A study that tested differences in selective attention among subgroups of ADHD indicated problems in early selective attention in children with SCT (n = 12; 7 ADHD/I and 5 ADHD/C) compared with children without SCT (n = 66; 9 ADHD/I, 23 ADHD/C, and 35 controls) (Huang-Pollock, Nigg, & Carr, 2005). However, there was no previously established cut-off level of SCT-symptoms dividing children with and without SCT, and the authors decided to include both ADHD/I and ADHD/C in the SCT group to increase power. In addition to the limited size of the SCT group, this makes the finding difficult to interpret. A recent study, controlling for the overlap with DSM-IV inattention symptoms, found that SCT was related to problems in sustained attention (Wahlstedt & Bohlin, 2010).

2 Objectives

The main objective of this thesis was to investigate the association between anxiety disorders and neurodevelopmental delays/disorders in children studied within a clinical setting. The more specific aims of investigation were:

- To compare the frequency and degree of motor impairment in a clinical sample of children with anxiety disorders, ADHD, and comorbid anxiety disorders and ADHD, compared with non-referred controls (paper I).
- To compare the frequency and degree of language impairment in a clinical sample of children with anxiety disorders, ADHD, and comorbid anxiety disorders and ADHD, compared with non-referred controls (paper II).
- To evaluate how anxiety symptoms, ADHD symptoms, and language ability predict social skills in a clinical sample of children with anxiety disorders with and without comorbid ADHD (paper II).
- To investigate the relationship between anxiety disorders, ADHD, and SCT in a clinical sample of children with anxiety disorders, ADHD, and comorbid anxiety disorders and ADHD, compared with non-referred controls (paper III).
- To explore the association between SCT and some selected neurocognitive measures in a clinical sample of children with ADHD with and without comorbid anxiety disorders (paper III).

3 Material and methods

3.1 The research group

An important basis for the current research has been a highly competent, well functioning research group. The group consisted of:

- Hanne Kristensen, MD PhD, project leader, head of RBUP's clinical research department, and child and adolescent psychiatrist at Nic Waal's institute.
- Beate Ørbeck, PhD, neuropsychologist, post doctoral research fellow at RBUP.
- Berit Hjelde Hansen, PhD candidate at RBUP, child and adolescent psychiatrist at Lillestrøm BUP.
- Benedicte Skirbekk, PhD candidate at RBUP, specializing in child and adolescent psychiatry at Nic Waal's institute.

3.2 Considerations concerning study design

The study is a clinical case-control study. In case-control studies, subjects with a given condition (cases) are identified and compared to subjects without the condition (controls) with regard to present or prior characteristics or exposures. Case-control studies are regarded as valuable when studying conditions with low prevalence. This type of study is manageable for a small research group with limited economical resources.

To learn more about neurodevelopmental problems in children with anxiety disorders we wanted to compare them not only to healthy controls, but also to a group of referred children where neurodevelopmental problems were known to be prevalent. We therefore decided to include children with ADHD as a contrast group. Due to the prevalent comorbidity between anxiety disorders and ADHD we allocated children with comorbid anxiety and ADHD to a separate group, instead of including them in the anxiety disorders group. However, including several groups also increases the number of participants needed, as multiple groups open for multiple intergroup comparisons, which again necessitates post hoc corrections of p-values to prevent Type I errors.

When planning the study, we conducted a pilot study in February 2006, reading through all referrals of children aged 7-12 years to the two included clinics, during a three week period, to evaluate the frequency of children with symptoms of anxiety disorders

referred to the clinics. We used this information, together with the prevalence of motor impairment found in dr. Kristensen's research on a population based sample of children with social phobia (Kristensen & Torgersen, 2008), to calculate the sample size needed for a power of 80% and a significance level of 0.05, and to calculate the study period needed to obtain this sample size.

This pilot study also reinforced our impression that reasons for referral were diverse and difficult to categorize, as the referrals did not need to include any suggestion of diagnosis, only a description that rendered it likely that the child was impaired by some kind of mental health problem. When planning the study we therefore decided to interview parents of *all* referred children in the relevant age group with the Kiddie-SADS, and use the diagnosis from the interview as inclusion criteria.

Hanne Kristensen had previously established contact with professor Katharina Manassis, a child and adolescent psychiatrist and director of the Anxiety Disorders Department at Hospital for Sick Children in Toronto, Canada. Professor Manassis accepted an invitation to collaborate with our group, and Kristensen, Ørbeck and Hjelde Hansen went to Canada to discuss the project design with her. After their return we compiled a comprehensive neuropsychiatric test battery, and started rehearsing the test procedures. In addition some colleagues and friends allowed us to apply the test battery on their children, to evaluate feasibility.

We decided that it would be advisable to include a third clinic to be able to limit the period of data collection to 18 months. The two clinics we already had decided to include were well known to us, and we to them, as Hjelde Hansen worked at Lillestrøm BUP and Kristensen and Skirbekk worked at Nic Waal's Institute. Most important, the clinics were general, outpatient child and adolescent psychiatric clinics, which, as far as we know, did not attract special subgroups of patients. The clinic leaders had agreed to implement Kiddie-SADS as standard initial assessment of all referred children in the relevant age group and agreed that the interviews could be conducted by the a member of the research group. We managed to find a third clinic that was initially interested in collaborating with us. However, they later decided to withdraw from the collaboration as they did not find it feasible to include the parent part of the diagnostic interview Kiddie-SADS as standard assessment of all referrals in the relevant age group. To increase recruitment in the remaining clinics we expanded the age-span to include 7-13 year old children. In March 2007 we conducted a new pilot study to evaluate the feasibility of the initial diagnostic assessment procedure in the two clinics. We found the procedure proved to be hard work, but feasible. We also

experienced that in most cases the mother came alone or the parents came together to the Kiddie-SADS interview. It rarely occurred that fathers came alone.

3.3 Participants

3.3.1 The clinical groups

The clinical sample consisted of 105 children aged 7 – 13 years, including 41 children with anxiety disorders (27 boys, 14 girls), 39 children with ADHD (30 boys, 9 girls), and 25 children with comorbid anxiety disorder and ADHD (12 boys, 13 girls) (Table 1). The children were recruited from referrals to two Norwegian outpatient child and adolescent psychiatric clinics over a 17-month period (autumn 2007 to spring 2009).

The inclusion/exclusion criteria

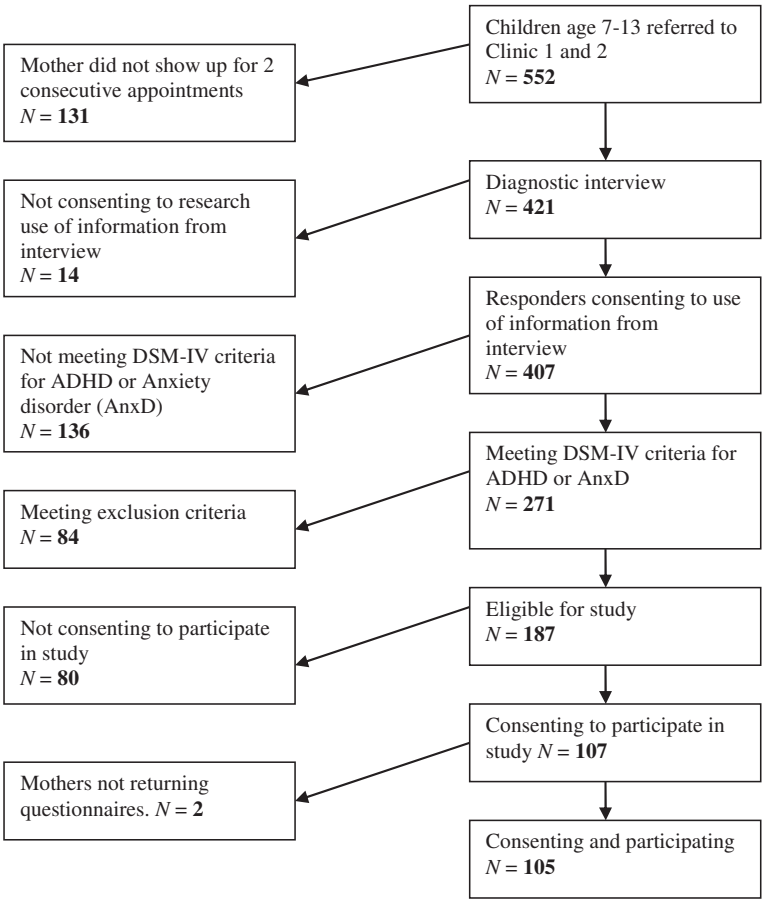
Children who, according to Kiddie-SADS interview, met the DSM-IV diagnostic criteria for any current anxiety disorder or ADHD, and who did not meet exclusion criteria, were invited to participate (n = 187). Due to feasibility only information from the mother was scored. Of the eligible children a total of 105 children participated in the study (Figure 1). A more detailed presentation of the inclusion procedure is provided in section 3.4.1.

The following predetermined exclusion criteria were used, resulting in the exclusion of a total of 84 children (number of children excluded in parenthesis):

- Biological mother not available (e.g., child adopted, n = 16). This exclusion criterion was selected because a research question in the main study concerns temperamental/personality measures in anxious children and their biological parents.
- Mother did not speak sufficient Norwegian to complete questionnaires (n = 19). This exclusion criterion was selected because several of the assessment measures were not available in the relevant languages.
- Child had IQ below 70 (n = 9). This exclusion criterion was selected because the interpretation of several of the assessment measures requires an IQ within the normal range.

- Child was on medication for ADHD (n = 16). This exclusion criterion was selected because ADHD-medication probably interferes with neuropsychological functioning.
- Child had a known neurological disease (n = 4). This exclusion criterion was selected because neurological disease is a well known cause of neurodevelopmental disorders.
- Child met DSM-IV criteria for Asperger Syndrome (n = 12). This exclusion criterion was selected because Asperger Syndrome is known to be associated with neurodevelopmental disorders.
- Child had ADHD and a history of AnxD or subthreshold AnxD, but did not meet DSM-IV criteria for a current AnxD (n = 8). This last exclusion criterion was selected to ensure that the 'pure' ADHD group did not include children with subthreshold anxiety.

Figure 1 Flowchart Showing Recruitment Into the Study



3.3.2 The control group

The control group was a convenience sample consisting of 36 non referred children, aged 7-13 years; 21 boys and 15 girls. Further details on recruiting procedures are provided in section 3.4.2.

The inclusion/exclusion criteria

On group level the children in the control group were matched with the children in the anxiety disorders group for age, gender and socio-economic status (SES). The SES level was categorized according to educational level. In 2-parent families the higher rated educational level was used.

Children were not included in the control group if they had been referred to mental health services or to the school psychological services, or if they had a present or prior anxiety disorder or ADHD according to Kiddie-SADS interview with the mother.

Table 1 Sample Characteristics

Group	AnxD	ADHD	AnxD + ADHD	Nonreferred controls
n	41	39	25	36
Age, mean (*SD*)	10.9 (2.0)	9.8 (1.6)	10.1 (1.9)	10.7 (2.3)
Boys/Girls	27/14	30/9	12/13	21/15
CGAS, mean (SD)	51.3 (6.2)	52.6 (5.1)	49.9 (5.6)	89.0 (6.1)
ADHD/I	–	17	12	_
ADHD/C	_	21	11	_
ADHD/H	_	1	2	_
Separation anxiety	15	_	12	_
Specific phobia	10	_	10	_
Social phobia	16	_	3	_
GAD	6	_	2	_
Panic disorder	2	_	_	_
Agoraphobia	2	_	1	_
OCD	10	_	4	_

AnxD, anxiety disorder; ADHD, attention deficit/hyperactivity disorder; SD, standard deviation; ADHD/I, ADHD/inattentive type; ADHD/C, ADHD/combined type; ADHD/H, ADHD/hyperactive type; GAD, generalized anxiety disorder; OCD, obsessive/compulsive disorder.

3.4 Sampling procedures

3.4.1 The clinical groups

The leaders of the participating clinics agreed Kiddie-SADS to be applied as standard assessment of all referred children aged 7-13 years, and to be done before the initiation of other assessment or treatment. To increase reliability the interviews were conducted by members of the research group. Ideally interviews should have been conducted with each of

the parents separately and with the child. This was not feasible with the available resources. As experience indicated mothers were more frequently attending the clinic than fathers, we decided the most uniform manner to conduct the interviews was by using the information from mothers when scoring the interviews. For the same reasons mothers were used as parental informants in the main study. Each of the clinics had a weekly meeting to evaluate new referrals. A member of the research group attended the meetings and assured appointments for Kiddie-SADS interview were sent to parents of all children aged 7-13 years. Subsequently the medical doctors Hanne Kristensen, Berit Hjelde Hansen, and I conducted Kiddie-SADS interviews with the parents of 421 children. If the parents allowed it, the interview was audiotaped for reliability testing. Some parents had to be interviewed separately due to a high level of conflict between them, others had to be interviewed with an interpreter due to insufficient Norwegian language skills. As the interview was part of the clinics standard assessment during the project period, an abstract and conclusion of each interview had to be noted in the patient record. The parents were asked for consent to use the information from the interview for research purposes. If they consented, the interview was immediately evaluated for inclusion/exclusion criteria. If the child was eligible for the study, the parents received written information about the project. Inclusion depended on written, informed consent from parents in addition to written informed consent from children 12 years or older, and verbal, informed consent from children younger than 12 years. If consenting to participate, a new appointment was made. At this appointment the child went through a comprehensive test battery, taking 3-4 hours including breaks, conducted by Berit Hjelde Hansen, neuropsychologist Beate Ørbeck, or me. The mother was sitting in an adjacent room filling out questionnaires. Before the mother and child left the clinic, the researcher looked through the questionnaires to assure completeness of the data. Questionnaires for the teacher were conveyed by the mother along with a prepaid return envelope. In case of missing items, the teachers were contacted by phone and scoring of the missing items obtained. If the parents wanted, which they all did, a short report of the findings from the assessment measures frequently used in clinical assessment (e.g. M-ABC and WASI) was included in the child's patient record, as were copies of questionnaires frequently used in the clinics (e.g. ADHD rating scale from mothers and teachers). Due to the described procedure, the researchers who tested the child were not always blind to the diagnoses obtained in the Kiddie-SADS interview. In addition, we were all experienced clinicians and would be expected to in general be able to tell a child with anxiety disorder

from a child with ADHD after spending several hours with them. However, we were blind to the questionnaires filled out by mothers and teachers.

3.4.2 The control group

The inclusion of controls was conducted immediately after inclusion of the clinical sample was terminated. The ideal recruitment of controls would have been to draw controls randomly from the total child population. However, as we needed the teachers of the included children to fill out several questionnaires, we assumed this was not feasible without approval from the school management. When we planned the study, we wanted to contact the schools in the regions served by the included clinics, and then send the invitation to participate to all children aged 7-13 in the schools consenting to participate. Then we could draw participants randomly from children who conformed to the inclusion/exclusion criteria. However, the Regional Committee for Medical and Health Research Ethics (REK) did not allow this. The procedure allowed by REK was that we contacted the school management and asked them to convey the invitation to the parents of a 'fairly typical', non-referred child of a specific age, gender and SES. The head master or social teacher then contacted a relevant teacher who sent the invitation home with the student. If they wanted to participate, the parents returned the consent form and contact information to the teacher, who in turn passed it on to the project leader. The SES level turned out to be the most difficult characteristic to match as the teachers hardly knew the parents occupation, and definitely not their educational level. When the consent form had been returned the project leader contacted the mother of the child and made an appointment for conducting the Kiddie-SADS interview. Questionnaires were sent to the mother, for her to fill in and bring with her to the appointment. After conducting the Kiddie-SADS interview, a member of the research group looked through the assessment forms together with the mother, to assure completeness of the data. The child was assessed at school during an ordinary school-day. Questionnaires were handed to the teacher along with a prepaid return envelope. In case of missing items the teachers were contacted by phone and scoring of the item obtained.

3.5 Missing data

Due to meticulous monitoring of incoming questionnaires, missing data were generally limited. All children completed the assessment battery. The missing data are described in the different papers.

3.6 Measures

The instruments used in the present study are described below. An important challenge was to select feasible assessment of diagnoses, cognition, language skills, motor skills, and social skills. Ideally the assessment should be standardized, internationally recognized and applicable to the included age span.

Kiddie-SADS P/L: Diagnoses were obtained by interviewing mothers with the Schedule for Affective Disorders and Schizophrenia for School-Aged children (6-18 years): Present and Lifetime Version (Kiddie-SADS P/L) (Kaufman, Birmaher, Brent, & Rao, 1997). We used the revised version, which includes the assessment of pervasive developmental disorders. All interviews were administered by the authors, who are all experienced clinicians. Inter-rater reliability was assessed by rescoring audiotapes from 39 random interviews. This resulted in kappa = 0.90 for ADHD and kappa = 0.88 for any AnxD.

CGAS: The Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983) was scored by the interviewer directly after the Kiddie-SADS interview. The CGAS is a well-known scale, with scores ranging from 1 (lowest functioning) to 100 (excellent functioning).

Disruptive Behavior Rating Scale (DBRS): To measure symptoms of attention problems and hyperactivity/impulsivity, we used the ADHD items from the DBRS (Barkley & Murphy, 1998), mother and teacher form. The rating scale contains the 18 items included in the DSM-IV diagnosis of ADHD, which are rated on a four-point scale (0 = never, 1 = sometimes, 2 = often, and 3 = very often). The scores were summed up to an ADHD symptoms score (used in paper II). In addition, two sub-scores were computed: Inattentive score (IA) and hyperactive/impulsive score (HI) (used in paper III). A high internal consistency has been demonstrated for this scale (Gomez, 2007). The internal consistency (Cronbach's alpha) of the scales in the present study were: 0.95 for mother-rated total score, 0.94 for mother-rated IA, 0.92 for mother-rated HI, 0.96 for teacher-rated total score, 0.94 for teacher-rated IA, and 0.94 for teacher-rated HI.

Children's Communication Checklist (CCC-2): The participants' use of language in their everyday life was assessed using the CCC-2 (Bishop, 2003), completed by mothers. The CCC-2 contains 70 items grouped into 10 subscales. Each item is rated on a four-point

frequency scale. As an overall measure of communication skills, a General Communication Composite (GCC) is calculated by summing the scaled scores of the first eight subscales (A–H). In addition, a Social Interaction Deviance Composite (SIDC) is calculated by subtracting the sum of the scaled scores of Scales A, B, C, and D from the sum of Scales E, H, I, and J. The GCC is designed to identify children with specific LIs, while the SIDC identifies children with pragmatic LIs disproportionate to their structural language abilities. A cut-off at the 10th percentile of the GCC discriminates between children likely to have clinically significant communication problems and typically developing children (Bishop, 2003; Helland, Biringer, Helland, & Heimann, 2009). The CCC-2 has been shown to provide a useful screening measure for communication impairment (Norbury, Nash, Baird, & Bishop, 2004), as has the Norwegian translation (Helland, Biringer, Helland, & Heimann, 2010). The internal consistency (Cronbach's alpha) of the GCC in the present study was 0.94. The Cronbach's alpha for the subscales A-J respectively were: 0.62, 0.61, 0.77, 0.84, 0.82, 0.61, 0.72, 0.70, 0.72, and 0.68. The CCC-2 scores were used in paper II.

Social Skills Rating Scale: The children's social skills were evaluated using the social skills items from the SSRS (SSRS) (Gresham & Elliott, 1990), parent form. The SSRS contains 38 social skills items, originally rated on a three-point frequency scale (0 = never, 1 = sometimes, 2 = very often). In our study, the items were rated on a four-point scale, including "often", to achieve a better distribution of scores. The scores were summed to form an SSRS total score. The SSRS has been shown to have good reliability and validity (Demaray et al., 1995). The internal consistency (Cronbach's alpha) of the SSRS in the present study was 0.91. The SSRS score was used in paper II.

Sluggish Cognitive Tempo 17 items scale (SCT-17): To assess symptoms of sluggish cognitive tempo, we used a 17-item SCT scale (Pfiffner et al., 2007). The items were rated by mothers on a four-point scale (0 = never, 1 = sometimes, 2 = often, and 3 = very often). The scores were summed up to obtain an SCT-17 total score. Data on reliability and validity are not previously published. The internal consistency (Cronbach's alpha) of the SCT-17 scale in the present study was 0.93. The SCT-17 total score was used in paper III.

Sluggish Cognitive Tempo 5 items scale (SCT-5): In addition to SCT-17, we used five SCT items that were evaluated recently to cover those used in previous research (Hartman, et al., 2004). These five items were assessed using a four-point scale (0 = never, 1 = sometimes, 2

= often, and 3 = very often). The scores were summed up to obtain an SCT-5 total score. Data on reliability and validity are not previously published. The internal consistency (Cronbach's alpha) of the SCT-5 scale in the present study was 0.83. The SCT-5 total score was used in paper III.

The Multidimensional Anxiety Scale for Children, short version (MASC-10): A children's self-report on anxiety was obtained using the 10-item version of the MASC, a widely used questionnaire for anxiety symptoms in children and adolescents (March, Parker, Sullivan, Stallings, & Conners, 1997). The MASC-10 has shown satisfactory reliability (March, Sullivan, & Parker, 1999). The internal consistency (Cronbach's alpha) of the MASC-10 in the present study was 0.76. The MASC-10 was used in paper II.

The Wechsler Abbreviated Scale of Intelligence (WASI): The intelligence quotient (IQ) was assessed using the WASI (Wechsler, 1999). The WASI provides a brief assessment of IQ and has shown high internal and external validity (Canivez, Konold, Collins, & Wilson, 2009). The WASI consists of two subtests assessing verbal IQ (Vocabulary and Similarities) and two subtests assessing performance IQ (Block Design and Matrix Reasoning). WASI is made for the age group 6-89 years and has age adjusted t scores for the sub-tests, verbal IQ, performance IQ and total IQ. For WASI the terms verbal-IQ and performance-IQ are somewhat misleading, since sub-tests of concentration and speed are not included. Verbal Understanding and Perceptual Organization are more precise terms, because the tests included here are identical to the other Wechsler IQ tests with these terms. The WASI "Verbal IQ" is thus a pure verbal measure. The WASI was used in all three papers.

The Movement Assessment Battery for Children (M-ABC): Motor impairment was assessed using the M-ABC (Henderson & Sugden, 1992). The M-ABC is one of the few motor assessment batteries available in a Nordic language and is well known in Norwegian clinics. The M-ABC is divided into four age bands from 4 to 12 years of age (the three age bands from 7 to 12 years were used in this study). Each age band covers the same types of skills and assesses motor impairment in three areas: manual dexterity (three tasks), ball skills (two tasks), and static and dynamic balance (three tasks). Raw scores on each item are converted to age-normed scores, ranging from 0 to 5. Normed scores are summed to form three subscale scores and a total score. The total score ranges from 0 to 40, where higher scores represent greater impairment. The M-ABC is widely used and recommended in the

assessment of motor impairment in children both in research and clinical practice (Geuze, Jongmans, Schoemaker, & Smits-Engelsman, 2001), and has shown moderate to good interrater and test-retest reliability (Smits-Engelsman, Fiers, Henderson, & Henderson, 2008). A cut-off at the normed 5th percentile is regarded as a strict cut-off point reducing the risk of false positives, and is regularly used to identify children with Developmental Coordination Disorder (DCD) in research (Geuze, et al., 2001). The M-ABC is used in paper I.

Reaction time: Reaction time was obtained using the computer-based Attention Network Test (ANT) (Rueda et al., 2004). The ANT consists of a fixation cross on the computer screen; a single fish or a horizontal row of five fish is presented above or below the fixation cross. The child is told to help us feed the central fish by pressing the mouse key corresponding to the direction in which the central fish is swimming. The central fish may appear alone (neutral trial), with flanking fish swimming in the same direction (congruent trial), or with flanking fish swimming in the opposite direction (incongruent trial). The appearance of the fish is preceded by one of four warning cue conditions: 1. a center cue (i.e., an asterisk is presented in the place of the fixation cross); 2. a double cue (i.e., asterisks are presented below and above the fixation cross); 3. a spatial cue (i.e., an asterisk is presented at the location of the upcoming fish); or 4. absence of cue. Correct responses are followed by an animation where the central fish blows bubbles, which is accompanied by a "woohoo!" sound. Incorrect responses are followed by a single tone and no animation. The median reaction time of correct responses (regardless of flanker type and warning cues) was used as a measure of cognitive tempo. Individual standard deviation (SD) was used as a measure of reaction time variability. The ANT differentiates children with ADHD from control children on a number of measures, including reaction time (Johnson et al., 2008). The reaction time measures are used in paper III.

Verbal memory: Verbal memory span and working memory were assessed using the Digit Span subtest of the WISC-III (Wechsler, 1991). The Digit Span test consists of a forward and a backward test. In the forward condition, the child is asked to repeat numbers verbatim as stated by the examiner. Digits are presented at a speed of one digit per second. The examiner starts by presenting a sequence of two digits. After the child has tried to reproduce the sequence, a new two-digit sequence is presented. If the child succeeds in reproducing at least one of the sequences, the number of digits presented is increased by one, with two

trials at each difficulty level, until the child fails to reproduce both trials at the same level. One point is given for each sequence that was recalled correctly. In addition, the maximum number of digits recalled is noted as a measure of maximal verbal memory span. In the Digit Span backward condition, which was administered and scored using the same procedure applied in the forward condition, the child is asked to reproduce the sequence in reverse order. As the backward condition requires manipulation of the recalled sequence, it is considered a measure of verbal working memory. In general, measures of variability are not calculated for the WISC-III Digit Span test. To obtain a measure of variability, we calculated the ratio between the total score obtained for each child and the possible maximum score of the child (i.e., (n correctly recalled sequences forward + n correctly recalled sequences backward)/(total number of sequences presented, with the exception of sequences at the level where the child failed both trials). The lowest degree of variability was obtained by the child reproducing every trial correctly, until the difficulty level at which the child failed both trials, and was reflected in a verbal memory variability score = 1. The highest degree of variability was obtained by the child reproducing only one trial correctly at each level, until the level at which the child failed both trials, and was reflected in a verbal memory variability score = 0.5. Hence, increased variability was reflected by lower scores. The WISC-III subtests have been validated in children with ADHD (Snow & Sapp, 2000). The measures of verbal memory were used in paper III.

Spatial memory Spatial memory span and working memory were assessed using an adaptation of the Finger Windows subtest from the Wide Range Assessment of Memory and Learning (WRAML) (Sheslow & Adams, 1990). The original version of the Finger Windows subtest was used previously in a study of cognition in anxious children with ADHD (Manassis, Tannock, Young, & Francis-John, 2007). The testboard consists of an 8 × 11-inch card with nine holes spaced randomly (“windows”), in which a pencil is inserted and the child is required to reproduce exactly the sequence of “windows” presented by the test administrator (forward condition), or in reverse order (backward condition). Our adaptation of the test was performed to render its administration similar to that of the WISC-III Digit Span subtest. Compared with the administration of the Digit Span test, the original Finger Windows test puts more strain on the child’s attention due to the increased and uneven number of trials at each sequence presented. We wanted to compare more directly verbal and visual/spatial memory by using tests with approximately the same workload for the child. Hence, in our adapted version of the Finger Windows subtest, the number of trials

at each difficulty level was reduced to two, starting with two holes as the simplest level. In the Finger Windows forward condition, the examiner inserts a pencil through a series of holes at a speed of one hole per second. The child is asked to reproduce the sequence exactly by putting his or her finger through the windows. The examiner starts by presenting a sequence of two holes. After the child has tried to reproduce the sequence, a new two-hole sequence is presented. If the child succeeds in reproducing at least one of the sequences, the number of holes presented is increased by one, with two trials at each difficulty level (our adaptation), until the child fails to reproduce both trials at the same level. One point is given for each sequence that was recalled correctly. In addition, the maximum number of windows recalled is noted as a measure of maximal spatial-memory span. In the Finger Windows backward condition, which was administered and scored using the same procedure applied in the forward condition, the child is asked to reproduce the sequence in a backward order. As the backward condition requires manipulation of the recalled sequence, it is considered a measure of spatial working memory. In general, measures of variability are not calculated for spatial-memory tests. To obtain a measure of variability, we followed the same procedure that was used for verbal memory. The measures of spatial memory were used in paper III.

3.7 Statistics

The statistical methods applied are described in more detail in the various papers. In all papers the Statistical Package for Social Sciences (SPSS), versions 15.0 and 18.0 for Windows, were used for statistical data analyses. In addition, the R (R Development Core Team, 2010) was used for some of the analyses in papers II and III. The description of the sample in the papers was done by Chi-square tests (for categorical data), independent samples T-tests, and analyses of variance.

When exploring the main objectives, analysis of variance (papers II and III) and covariance (papers I and II) were used to compare means between different groups. To evaluate group differences in subscale means we used a linear mixed effects model (Pinheiro & Bates, 2000) (paper II). Linear regression was used to evaluate relationships between variables, as the relevant dependent variables were continuous (papers II and III).

When relevant, p-values were corrected for multiple comparisons to reduce the risk of type I errors. All presented p-values are two-tailed.

3.8 Ethical aspects of the study

The present study was approved by the Regional Committee for Medical and Health Research Ethics. Children who were 12 years or older, and the parents of all invited children received written information about the study. All invited subjects were informed that whether they consented or declined would not affect the services provided by the clinic. Children younger than 12 years received verbal information from the researcher before starting the assessment. Written consent was obtained from all parents and all children aged 12 years or older participating in the study.

4 Summary of results

4.1 Papers I –III

All three papers are based on the same participants: 141 children aged 7 – 13 years, including 41 children with anxiety disorders (27 boys, 14 girls), 39 children with ADHD (30 boys, 9 girls), 25 children with comorbid anxiety disorder and ADHD (12 boys, 13 girls), and 36 non referred children (21 boys, 15 girls).

Paper I *Motor impairment in children with anxiety disorders*

The purpose of this paper was to examine the prevalence and degree of motor impairment in referred children with anxiety disorders, compared with children with ADHD, children with comorbid anxiety disorders and ADHD, and non-referred controls. Diagnoses were obtained by the semi-structured diagnostic interview Kiddie-SADS. Motor performance was assessed using the Motor Assessment Battery for Children (M-ABC).

In this study, we found that children with anxiety disorders exhibited significantly higher motor impairment scores than controls, but they were not significantly different from children with ADHD or children with comorbid anxiety disorder and ADHD. All clinical groups exhibited similar profiles of motor impairment, which does not support the assertion in recent literature of more balance problems among children with anxiety disorders. A total of 19 (46%) children with anxiety disorders, without comorbid ADHD, scored below the normed 5th percentile on the M-ABC, indicating that motor function is impaired in many referred children with anxiety disorders to a degree that may interfere with their activities of daily living. These findings support the notion that neurodevelopmental disorders (in the present paper conceptualized by motor impairment) are prevalent in referred children with anxiety disorders, and that assessment of motor function is important in understanding the daily challenges of these children.

Paper II *Language impairment and its relationship with social skills in children with anxiety disorders*

The purpose of this paper was to examine the prevalence and profile of language impairment in referred children with anxiety disorders, compared with children with ADHD, children with comorbid anxiety disorders and ADHD, and non-referred controls. Furthermore we wanted to evaluate how language skills relate to social skills in children with anxiety disorders with or without comorbid ADHD. Diagnoses were obtained by the semi-structured diagnostic interview Kiddie-SADS. Language skills were assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) and the Children's Communication Checklist (CCC-2), and social skills were measured with the Social Skills Rating System (SSRS). Differences in GCC were adjusted for IQ.

Children with anxiety disorders had significantly lower mean verbal IQ scores than controls, but they were not significantly different from children with ADHD or children with comorbid anxiety disorder and ADHD. Measured by the General Communication Composite (GCC) of the CCC-2, half of the children in the anxiety disorders group exhibited language skills below the 10^{th} percentile, indicating language impairment. On the CCC-2, children with anxiety disorders exhibited significantly poorer GCC scores than controls, but significantly better scores than children with ADHD and children with the comorbid condition. Hierarchical linear regression analysis revealed that the social skills of the children with anxiety disorders, with or without comorbid ADHD, were related to language skills rather than to the children's degree of anxiety or ADHD symptoms. These findings support the notion that neurodevelopmental disorders (in the present paper conceptualized by language impairment) are prevalent in referred children with anxiety disorders, and that assessment of language skills is important in understanding the daily challenges of these children. Furthermore, the findings suggest that when evaluating social skills in children with anxiety disorders it would be advisable to consider the impact of language skills.

Paper III *The relationship between sluggish cognitive tempo, subtypes of attention-deficit/hyperactivity disorder, and anxiety disorders*

The purpose of this paper was to examine the relationship between sluggish cognitive tempo (SCT), anxiety disorders, and subtypes of ADHD in referred children with anxiety disorders, children with ADHD, children with comorbid anxiety disorders and ADHD, and non-referred controls. Furthermore we wanted to explore the relationship between SCT and some candidate neurocognitive measures (reaction time, verbal memory, and spatial memory). Diagnoses were obtained by the semi-structured diagnostic interview Kiddie-SADS. SCT was assessed by a questionnaire filled in by the mother. Neurocognitive measures were obtained by testing the child, and are more thoroughly described in the paper.

We found significant differences in the levels of SCT among the four main groups, with comorbid anxiety disorders and ADHD > ADHD > anxiety disorders > controls. The difference in levels of SCT between the two latter groups was no longer significant after adjusting for the level of DSM-IV inattentive symptoms. Furthermore, we found that SCT correlated significantly with inattentiveness, and that children with ADHD/I and ADHD/C did not exhibit significantly different levels of SCT. The exploration of neurocognitive measures revealed that SCT correlated with variability in spatial memory; in contrast, there was no correlation between SCT and reaction time. These findings support the notion that the concept of SCT may capture important differences between subgroups of children with ADHD. However, in our study these differences did not relate to the subtypes of ADHD (i.e. ADHD/I vs ADHD/C), but rather to the subgroups ADHD with comorbid anxiety disorder vs ADHD without comorbid anxiety disorder.

4.2 Motor impairment and language impairment taken together

In papers I and II the prevalence of motor impairment and the prevalence of language impairment are presented separately. As the main objective of the present thesis was to investigate the association between anxiety disorders and neurodevelopmental delays/disorders in children, I found it interesting to evaluate these two neurodevelopmental problems together.

Defining the presence of a neurodevelopmental disorder as exhibiting an M-ABC total score at or below the 5th percentile (as done for motor impairment in paper I) or a GCC score at or below the 10th percentile (as done for language impairment in paper II) of the general population, we can create the following table (Table 2):

Table 2 Cross-tabulation of neurodevelopmental disorders for each group of children

	AnxD	ADHD	AnxD + ADHD	Controls	Total
Motor impairment, *n (%) (paper I)*	19 (46.3)	10 (25.6)	9 (36.0)	2 (5.6)	40 (28.4)
Language impairment, *n (%) (paper II)*	20 (50.0)	23 (60.5)	19 (76.0)	4 (11.1)	66 (47.5)
NDD, *n (%)*	26 (63.4)	27 (69.2)	22 (88.0)	6 (16.7)	81 (57.4)
Not NDD, *n (%)*	15 (36.6)	12 (30.8)	3 (12.0)	30 (83.3)	60 (42.6)
Total, *n*	41	39	25	36	141

NDD, Neurodevelopmental disorder; AnxD, anxiety disorder; ADHD, attention deficit/hyperactivity disorder.

Exact chi-square test of the cross-tabulation of neurodevelopmental disorder and group was significant (χ^2 (3, n = 141) = 36.850, $p < 0.001$). Post-hoc exact chi-square tests showed that all clinical groups were significantly different from the control group, but the clinical groups were not significantly different from each other (anxiety disorders vs ctrl, χ^2 (1, n = 77) = 17.248, $p < 0.001$; anxiety disorders vs ADHD, χ^2 (1, n = 80) = 0.302, $p = 0.641$; anxiety disorders vs comorbid anxiety disorders + ADHD, χ^2 (1, n = 66) = 4.733 , $p = 0.135$; ADHD vs ctrl, χ^2 (1, n = 75) = 20.992, $p < 0.001$; ADHD vs comorbid anxiety disorders + ADHD, χ^2 (1, n = 64) = 2.991, $p = 0.261$; comorbid anxiety disorders + ADHD vs ctrl, χ^2 (1, n = 61) = 30.233, $p < 0.001$). All p-values are two-sided and corrected for multiple comparisons by the Holm-method (Aickin & Gensler, 1996). These findings are discussed in section 5.2.

5 Discussion

5.1 Discussion of main results

The main finding of the present study is the high prevalence of neurodevelopmental disorders, as conceptualized by motor and language impairment, in referred children, aged 7 – 13 years, with anxiety disorders. In addition, an important finding is the elevated level of sluggish cognitive tempo among children with comorbid anxiety disorder and ADHD compared with children with ADHD without comorbid anxiety disorder.

5.1.1 Anxiety disorders and motor impairment

In the present study we found that children with anxiety disorders exhibited significantly poorer motor impairment scores compared with controls, after adjusting for differences in IQ and gender distribution. There were no significant differences between the clinical groups (i.e., anxiety disorders, ADHD, and comorbid anxiety disorders and ADHD). A substantial proportion (46%) of children with anxiety disorders, without comorbid ADHD, scored below the 5th percentile on the M-ABC.

The findings of more motor problems in children with anxiety disorders than in controls as well as the lack of group differences in motor problems between children with anxiety disorders and children with ADHD are in line with the findings in population-based studies (Ekornås, et al., 2010; Kristensen & Torgersen, 2008). However, establishing that there is a significant difference in mean motor impairment scores between a group of children with anxiety disorders and a control group does not automatically imply that motor impairment is an *important* problem among children with anxiety disorders, as motor impairment may occur with varying degrees of severity and varying implications for daily activities. The diagnosis of DCD (developmental coordination disorder) requires information about impaired 'performance in daily activities that require motor coordination' (American Psychiatric Association, 2000). Unfortunately, we did not have information about daily life activities in the present study, and accordingly we were not able to diagnose DCD. Still, it is possible to make some assumptions about the degree of motor impairment among children with anxiety disorders in the present study. According to a recent study, motor coordination below the 5th percentile represents a challenge in a multitude of daily activities, both at home and at school (Wang, et al., 2009). Hence, it is reasonable to assume that an M-ABC score below the 5th percentile represents a potential problem for the child. In the present study, we found 19 (46%) of the 41 children with anxiety disorders, without

comorbid ADHD, to exhibit motor coordination below the 5th percentile. This is in line with a recent study that found 12 (44%) out of 27 children with anxiety disorders in a community sample exhibited motor problems, as defined by M-ABC scores below the 5th percentile (Ekornås, et al., 2010). These findings indicate that substantial motor problems are frequent in children with anxiety disorders.

Some studies emphasize the finding of balance problems among both children (Erez, et al., 2004) and adults (Balaban & Jacob, 2001) with anxiety disorders, and suggest this finding implies a specific link between balance and anxiety. To support this suggestion one would need to demonstrate that subjects with anxiety exhibit more balance problems than other motor problems, and relatively more balance problems compared to subjects with other psychiatric conditions known to be related to motor problems (e.g., ADHD). In our study the three clinical groups exhibited approximately the same pattern of M-ABC subscale scores (i.e., manual dexterity, ball skills, and balance). This similarity of profiles between the clinical groups, together with the finding of significantly poorer manual dexterity scores among children with anxiety disorders compared with typically developing children, do not support the assumption of a specific link between balance and anxiety. Rather, this indicates children with anxiety disorders exhibit an elevated prevalence of complex motor impairment, as typically seen among children with DCD.

A child's motor ability may well have impact on their social skills. Indeed, this association has been addressed in recent research (Bart, Jarus, Erez, & Rosenberg, 2011; Lingam et al., 2010). Unfortunately, we did not consider the possibility of including measures of social skills when we prepared the paper about motor impairment.

5.1.2 Anxiety disorders and language impairment

In the present study we aimed to investigate language impairment in children with anxiety disorders. In addition, we wanted to explore the relationship between language skills and social skills in children with anxiety disorders. Our main findings were that all clinical groups exhibited poorer language skills than controls. Among children with anxiety disorders in our sample, including children with comorbid anxiety disorders and ADHD, social skills were mainly related to language skills, rather than to the level of anxiety or ADHD symptoms.

The finding that children with anxiety disorders exhibit both poorer verbal IQ scores and poorer scores on the CCC-2 (which assesses the child's use of language in everyday situations) than controls, indicates that poorer language skills among children with anxiety

disorders are not just test-room phenomena, but real life challenges. This is further underscored by the finding that children with anxiety disorders exhibit significantly poorer scores than controls on nine out of ten subscales of the CCC-2, demonstrating that a broad spectrum of communication skills is affected. A possible bias when comparing a clinical group with controls is that the detected differences are due to advantages of the control group rather than disadvantages of the clinical group (Coplan & Evans, 2009). We therefore found it interesting to relate our findings to the cut-off at the CCC-2 10th percentile, recommended used to identify children likely to have clinically significant communication problems (Bishop, 2003; Helland, et al., 2009). In the present study, half of the children in the anxiety disorders group and three-quarters of the children in the comorbid anxiety disorders and ADHD group exhibited CCC-2 scores consistent with clinically significant communication problems.

In the current study, we also wanted to investigate whether language skills in children with anxiety disorders were related to social skills. All three clinical groups exhibited poorer social skills, as assessed by the SSRS, than controls. To evaluate the relationship between language impairment and social skills in children with anxiety disorders, we included all children with anxiety disorders, with and without comorbid ADHD, in a linear regression analysis. Adjusting for gender, age, performance IQ, degree of ADHD symptoms (as assessed by teacher DBRS), and degree of anxiety symptoms (as assessed by child MASC-10), language skills was the only factor significantly related to social skills.

5.1.3 Anxiety disorders and attentional problems

In the present study we wanted to investigate the relationship between SCT (an assumed subtype of attentional problems), anxiety disorders, and subtypes of ADHD. In addition, we wanted to explore the relationship between SCT and some candidate neurocognitive measures.

Our main findings were that the four diagnostic groups exhibited significantly different levels of SCT with comorbid anxiety disorders and ADHD > ADHD > anxiety disorders > controls, while there were no significant differences in the levels of SCT between children with ADHD/I and children with ADHD/C. The difference in levels of SCT between the anxiety disorders group (without ADHD) and controls, was no longer significant after adjusting for the level of DSM-IV inattentive symptoms. The investigation

of neurocognitive measures revealed the presence of a significant relation between SCT and variable performance on a spatial memory test. In contrast, there was no correlation between SCT and reaction time.

The frequent comorbidity of anxiety disorders and ADHD is previously well described (Costello, et al., 2005; Schatz & Rostain, 2006). The design of the present study precludes evaluation of the prevalence of this comorbidity. However, by including children with anxiety disorders and children with comorbid anxiety disorders and ADHD, the present study provides a new perspective on the controversy regarding the utility and impact of SCT. Our finding of a higher level of SCT-symptoms among children with comorbid anxiety disorders and ADHD, in addition to the finding of a relationship between SCT and inattention symptoms, expands on previous research that found more anxiety among children with ADHD/I and high levels of SCT (Carlson & Mann, 2002; Hartman, et al., 2004). The lack of significant differences in levels of SCT between the anxiety disorders group (without ADHD) and controls when adjusting for the level of DSM-IV inattentive symptoms, indicates that the relationship between SCT and anxiety disorders (without comorbid ADHD) is mediated by inattentiveness. This leaves it less likely that there is a direct relationship between anxiety and SCT. Furthermore, our findings did not support the notion that SCT identifies a hypoactive subtype of ADHD/I (Carlson & Mann, 2002; Hartman, et al., 2004; McBurnett, et al., 2001). Rather, we found children with ADHD/I and ADHD/C to exhibit relatively similar levels of SCT. In addition, SCT-symptoms were significantly related to the degree of inattentive symptoms, but showed practically no relationship (neither direct nor inverse) with hyperactive/impulsive symptoms.

The finding that a higher level of SCT was related to more variability in spatial memory, but not to reaction time, may indicate that the concept of SCT reflects increased variability in attention rather than pure slow cognitive tempo. As the relationship between SCT and variability in spatial memory remains significant after adjusting for the degree of DSM-IV inattention symptoms, our findings support the hypothesis that the construct of SCT captures specific attention problems that are not described sufficiently by the nine attention symptoms included in the DSM-IV based ADHD diagnoses.

Taken together, our findings expand on previous research by demonstrating that children with comorbid anxiety disorders and ADHD exhibit more SCT symptoms than children with ‘pure’ ADHD, regardless of subtype of ADHD or degree of DSM-IV hyperactivity/impulsivity. If SCT is neither related to processing speed nor to the absence of

hyperactivity, it is tempting to suggest that 'Sluggish Cognitive Tempo' is a term that is somewhat misleading.

To explain the relationship between SCT and the comorbid condition one might speculate that the combination of ADHD and high levels of SCT involves an increased susceptibility to the development of anxiety disorders. Another possibility is that SCT reflects that the comorbidity with anxiety disorders in children with ADHD puts a strain on attention functions that are already susceptible, leading to a more overt impairment. However, as the design of the present study does not allow the analysis of causality, these speculations would need to be addressed in a longitudinal study

5.2 Anxiety disorders and neurodevelopmental delays/disorders

The three articles included in this thesis examine different areas of neurodevelopmental difficulties in referred children with anxiety disorders, compared with children with ADHD, children with comorbid anxiety disorders and ADHD, and non-referred controls.

The main findings are that referred children with anxiety disorders exhibit a high prevalence of neurodevelopmental disorders (as conceptualized by significant motor or language impairment), and that referred children with comorbid anxiety disorders and ADHD exhibit a higher level of SCT than children with ADHD alone.

As the main objective of this thesis was to investigate the association between anxiety disorders and neurodevelopmental delays/disorders in a clinical setting, the neurodevelopmental disorders have also been analyzed together. As shown in Table 2 (section 4.2), 63 % of the children in the anxiety disorders group and 88 % of the children in the comorbid anxiety disorders and ADHD group display at least one comorbid neurodevelopmental disorder. This is not significantly different from the 69 % found among the children in the ADHD group. In the control group, 17 % of the children exhibited at least one neurodevelopmental disorder. This is significantly less than in the clinical groups. Initially, 17 % may appear to be a high prevalence among the control children. However, in the control group there was no overlap between children exhibiting an M-ABC total score at or below the 5^{th} percentile (6 %) and children exhibiting a GCC score at or below the 10^{th} percentile (11 %), resulting in a pure additive effect in this group when analyzing neurodevelopmental disorders together. Though the prevalence of comorbid problems may be higher in clinical than population-based samples (Berkson, 1946), the frequency of motor impairment found in the present study is corresponding with the frequency found in a

community study (Ekornås, et al., 2010), while language impairment has, as far as I know, not been studied in community samples of children with anxiety disorders.

It is well known that the prevalence of comorbidity may be inflated in clinical samples, especially if both conditions are separate reasons for referral to the clinic, or the one condition increases the probability of referral of the other condition (Berkson, 1946). In the present study there was a non-significant tendency towards a higher prevalence of neurodevelopmental disorders among children with comorbid anxiety disorders and ADHD compared with the children with 'pure' conditions. This may be due to the mechanism described by Berkson, as both anxiety disorders and ADHD are separate reasons of referral to the clinic, and both of these groups of patients exhibit an increased prevalence of neurodevelopmental disorders. However, there is also a possibility that children with comorbid anxiety disorders and ADHD really do exhibit an increased prevalence of neurodevelopmental disorders, but this would need to be explored in a population-based sample.

The finding of an increased level of SCT among children with comorbid anxiety disorders and ADHD, relates to an ongoing controversy in the ADHD-field. However, the finding is also interesting in the study of anxiety disorders, as it leads to a couple of new questions regarding the comorbidity between anxiety disorders and ADHD. One question that arises is whether SCT represents a separate risk factor for the development of anxiety disorders among children with ADHD. Another question is whether the addition of an anxiety disorder in children with ADHD leads to exacerbation of attention problems by putting an extra strain on already susceptible attention functions. These questions would need to be addressed in a longitudinal study.

Taken together, there is a high prevalence of neurodevelopmental disorders among referred children with anxiety disorders. To my knowledge, the joint prevalence of motor and language impairment among children with anxiety disorders has not been presented previously. Hence, the current findings are in need of replication, both in clinical and community samples. However, the findings underscore the importance of addressing neurodevelopmental disorders in the assessment and treatment of children with anxiety disorders.

5.3 Methodological issues

5.3.1 Internal validity

When evaluating the validity of a study one commonly distinguishes between internal and external validity. A high internal validity requires that the data are properly collected (e.g., thorough procedures and good measures), analyzed and interpreted, and that the findings are representative of the population the participants are recruited from (Aalen & Frigessi, 2006). The internal validity may be affected by random and systematic errors. In epidemiological studies there are three main sources of systematic errors: Selection bias, information bias, and confounding (Grimes & Schulz, 2002).

Random error

Random errors represent an unpredictable variability in the data. As no sample will be exactly identical to the target population, the estimates we calculate will vary from sample to sample (sampling variation). This variation can be reduced by increasing the sample size. In statistical analysis, p-values and confidence intervals will be informative when evaluating the possibility that our finding is only due to random variation, and when evaluating how close the estimate made is to the value in the population. Random errors may also occur from unpredictable variability in measurement (random measurement variation). This type of random errors may be limited by increasing the precision of the measurement. In the present study we have tried to limit random measurement variation by using standardized assessment tools.

Selection bias

Selection bias refers to the situation where the participants in the study are systematically different from the population the findings in the study are intended to be generalized to. In the present study it would represent a selection bias:

- If the participants were significantly different from the eligible children not participating
- If the children referred to the clinic represented a special subgroup of cases
- If the controls did not come from the same population as the cases
- If the controls were not randomly drawn

To reduce the probability of skewed recruitment among referred children in the present study, inclusion and exclusion criteria were clearly defined before the recruitment started. These criteria were defined as strictly as possible. Parents of all referred children in the relevant age-group were interviewed with Kiddie-SADS at their first appointment at the clinic, to standardize the evaluation of eligibility. Invitation to participate in the study was administered to the parents of all eligible children. The children that consented to participate (n = 105) and those that declined participation (n = 82, including two individuals who initially consented, but failed to return questionnaires) did not differ in mean age, M (SD) = 10.3 (1.9) vs. M (SD) = 10.5 (1.9) years, t (185) = -0.588, p = 0.56; mean score on the Children's Global Assessment Scale (CGAS) (Shaffer, et al., 1983), M (SD) = 51.4 (5.7) vs. M (SD) = 51.1 (6.2), t (185) = 0.357, p = 0.72; or gender distribution, χ^2 (1, n = 187) = 0.906, p = 0.34.

To my knowledge, the included clinics admit all referred children who are considered to be in need of mental health care, and do not attract special subgroups of affected children. In 2008 Lillestrøm BUP served a community of 35.000 children aged 0-18 years and offered treatment to approximately 1.1 % of their child population, and Nic Waal's Institute served a community of 27.500 children aged 0-18 years and offered treatment to approximately 1.9 % of their child population. The Norwegian health system is public and there are barely any private alternatives within the field of child and adolescent psychiatry. This renders the total of children referred fairly representative of the population seeking child and adolescent psychiatric health care in the actual areas. However, some caution is needed due to the relatively large number of families not showing up for two consecutive appointments (n=131) (Figure 1). Unfortunately, we do not have any information about these children.

The control children were recruited from schools within the areas served by the included clinics. However, as described under sampling procedures, we did not manage to draw control children randomly from the child population. Hence, the control group was a convenience sample and thereby not representative for the child population. The anxiety group and the control group were not significantly different in gender distribution, mean age, or mean SES. A typical challenge with a convenience sample is that the children recruited to the control group are overly well functioning. However, when we contacted the schools we emphasized the importance of recruiting main stream students, hoping this would reduce this tendency. The findings that 5.6 % of the control children scored at or below the 5th percentile of the M-ABC, and 11.1 % of the control children scored at or below the 10th percentile on the GCC indicate that for measures of motor and language

impairment the control group did not differ substantially from what one would expect to find in the general child population. Though we have tried to mitigate the problems related to the non-random recruitment of the control group, it is important to acknowledge that it is still a convenience sample.

Information bias

Information bias refers to the error occurring when the information collected about or from the participants is incorrect. Examples of information biases are recall bias (cases remember past exposures more clearly than controls) and biased collection of information (the researcher is aware of who are cases and who are controls). Information bias may be reduced by combining several assessment methods (e.g., interviews, questionnaires, and tests) and several informants (e.g., study subjects, mothers, fathers, and teachers). A firm assessment procedure will reduce the risk of biased collection of information.

To make the recruitment procedure in the present study feasible, we had to decide on only one informant for the Kiddie-SADS interview. Due to the age of the participants we decided to use the parent interview. As our experience from the pilot study indicated that the mother was the parent who most frequently attended the interview, we decided to use the information from the mother when scoring Kiddie-SADS. Diagnostic information from other informants could potentially add symptoms not noted by the mother or even alter the interpretation/classification of a reported symptom (e.g., school refusal may result from peer victimization at school, from rigidity as in pervasive developmental disorders, from fear of attention from others as in social anxiety, or from fear of separation from parents as in separation anxiety). If we have overlooked symptoms that would have been reported by another informant, this may have lead to an underestimation of diagnoses, which again may have resulted in us failing to identify all eligible children.

The present study was not blinded. In several cases the one from the research group who tested the child was the same person that had interviewed the mother. In addition, as all members of the research group were experienced clinicians, it was in general not difficult for us to distinguish between a child with anxiety disorder and a child with ADHD in the test situation. Knowledge about the child's diagnoses could influence the testing of the child. To reduce the risk of such bias we followed a predetermined test-protocol.

To reduce other informant biases in the study, we have had a relatively strict assessment procedure and we have aimed to use the combination of several assessment

measures and several informants. However, the risk of information bias can never be ruled out.

Confounding

Confounding is when a variable is associated with the independent variable, and also affects the dependent variable (Kirkwood & Sterne, 2003). In some situations a confounder may mask the association between two variables or even suggest a difference in the opposite direction, in other situations a confounder may suggest an association were none exists. In the present study, we have controlled for well-known confounders like IQ and gender by including them in the analyses. This is more thoroughly described in the papers. However, it is important to remember that even though including suspected confounders in the analyses, there is always a possibility that important confounders have not been measured and subsequently they are not included.

Although some threats to internal validity cannot completely be ruled out, I consider that the present study has a sufficient internal validity to justify the generalization of the findings to the children referred to the included clinics. This makes it appropriate to evaluate the external validity of the study.

5.3.2 External validity

The external validity describes whether the findings of a study are applicable to subjects outside the study population. A high internal validity is a requirement for a study's external validity (Aalen & Frigessi, 2006).

The prevalence of a characteristic in a clinical population will not be representative of the prevalence in the general population. This is especially true if the characteristic by itself increases the probability for referral to the clinic (Berkson, 1946). E.g., one would expect the prevalence of comorbidity of anxiety disorders and ADHD to be inflated in a clinic where anxiety disorders and ADHD are separate reasons for referral. On the other hand, if the characteristic does not affect the probability for referral one would expect the characteristic to have a similar prevalence as in the general population. E.g., one would not expect the use of a special brand of tooth paste to be differentially distributed in the clinical and the general population. However, information about the prevalence of a characteristic in a clinical population is by itself interesting as it has the potential to increase knowledge about characteristics/comorbidities that may need clinical attention in their own right, or that may affect prognosis and/or treatment of the main condition. If the clinical population is

well described, it may be possible to generalize the findings to similar clinical populations. In my opinion, it is possible to generalize the present findings to similar clinical populations. However, caution is needed as cultural differences as well as differences in referral practices may pose a challenge for the comparability of clinical populations.

5.3.3 Strengths and limitations of the present study

A strength of the present study is the use of a carefully assessed clinical sample. Furthermore, the thorough recruitment and assessment procedures probably reduce the threats to internal validity. In addition, the objectives of the study are clinically relevant and may illuminate issues that are important in the assessment and treatment of children with anxiety disorders.

The present study also has limitations. The study was cross-sectional, precluding the analysis of any directional relationship between anxiety and neurodevelopmental disorders. In addition, the modest sample size restricts the possibility for subgroup analyses and increases the risk of type II errors. The assessment of the included children was not blinded. Furthermore, the control group was a convenience sample, and hence not representative for the general child population. Another limitation is that the psychiatric diagnoses were based on Kiddie-SADS interview with mothers only. The establishment of a diagnosis based on a single informant is not regarded best practice. Inclusion of diagnostic information from the child, the fathers, and the teachers would have improved the reliability of the diagnoses. There is a general problem of comorbidity in clinical populations. We have, to some extent, controlled for this by creating separate diagnostic groups, but there is always the possibility of other comorbid factors affecting our findings (e.g., dyslexia). Finally, the lack of information about the group of families not attending the initial appointment at the clinics is also a limitation.

Regarding motor impairment, the M-ABC does not cover the full range of motor abilities and the use of only one test may lead to an underestimation of motor problems. In addition, the lack of information about daily activities from interviews or questionnaires in the present study may have lead to an overestimation of motor problems, by assuming motor problems in children with test performance below the 5th percentile, but also to underestimation, by not recognizing motor problems in children with motor performance in the borderline area between the 5th and the 15th percentile.

In the study of language impairment, the CCC-2 was used as a screening measure for communication problems. Though it is a well respected measure it is not a direct measure of language abilities. It is advisable that future research include direct measures of language, both to be able to diagnose specific language impairment and to provide a description of the nature of the language impairment in anxious children.

Recent research has found an association between motor ability and social skills. It is a limitation to the present study that we did not study this association in our sample, and that we did not include motor ability as an independent variable in the regression analysis of factors associated with social skills in paper II.

5.4 Implications

5.4.1 Implication for clinical praxis

The finding of this high proportion of neurodevelopmental disorders among referred children with anxiety disorders is a powerful reminder of the importance of assessing neurodevelopmental disorders in these children. Neurodevelopmental disorders may hamper a child's development of independent mastery and restrict the child's opportunities for social interaction. Considering the notable proportion of children with anxiety disorders who exhibit substantial motor impairment, both in the present study and in population-based studies, assessment of motor ability in children with anxiety disorders should be routinely conducted. Likewise, though in need of replication, the finding that a high proportion of children with anxiety disorders exhibit significant language impairment, illuminates the importance of evaluating language skills in the clinical assessment of children with anxiety disorders. Knowledge of the child's motor and language ability is important to modify the demands of both everyday life and treatment programs to a level the child is able to handle. In addition, the neurodevelopmental disorders may require treatment interventions, independent of the anxiety disorder.

5.4.2 Implications for future research

The present thesis underscores the need of further research on neurodevelopmental disorders in both clinical and population-based samples. Furthermore, longitudinal studies are needed to analyze the direction of the relationship between anxiety disorders and neurodevelopmental disorders. Longitudinal research may also illuminate whether the presence of a neurodevelopmental disorder affects prognosis or treatment outcome of the

anxiety disorders. In addition, the findings in the present study underscore the importance of including measures of anxiety in future research on SCT, as anxiety may constitute an important confounder explaining the ambiguous findings in previous research regarding the relationship between SCT and the ADHD subtypes. Longitudinal research on children with ADHD could also evaluate the direction of the relationship between anxiety and SCT among these children.

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I

Paper I

Motor impairment in children with anxiety disorders

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This study examined the frequency and degree of motor impairment in referred children with anxiety disorders (AnxDs), compared with children with attention deficit/hyperactivity disorder (ADHD), children with comorbid AnxDs and ADHD, and nonreferred controls. All participants (n = 141; 90 males, 51 females; mean age: 10 years, 1 month; range: 7–13 years) had an IQ greater than 70. Diagnoses of mental disorders were established using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (Kiddie-SADS). Motor ability was assessed using the Movement Assessment Battery for Children (M-ABC). We found that children with AnxDs exhibited significantly higher total impairment scores on the M-ABC than controls, but were not significantly different from children with ADHD or children with comorbid AnxDs and ADHD. All clinical groups exhibited similar profiles of motor impairment. A total of 19 (46%) children with AnxDs scored below the 5th percentile on the M-ABC, indicating that motor function is impaired in many children with AnxDs to a degree that probably interferes with their activities of daily living. These results support the notion that assessment of motor function is important in understanding the daily challenges of children with AnxDs.

1. Introduction

The relationship between anxiety disorders (AnxDs) and motor impairment has attracted little attention in anxiety research, even though such a relationship has previously been observed (Shaffer et al., 1985; Pine et al., 1997). The authors of a recent review (Emck et al., 2009) found only two clinical studies (Baumann et al., 2004; Vance et al., 2006) between 1997 and 2007 that met their inclusion criteria of more than 30 participants, emotional problems or psychiatric disorders assessed by standardized diagnostic instruments, and measurements of gross motor performance of verifiable psychometric quality. In the first of these studies (Baumann et al., 2004), 102 inpatient children aged 5–13 years were divided into four subgroups of externalizing disorder, internalizing disorder, combined internalizing and externalizing disorder, and other disorders, based on diagnostic information from the children's psychiatric records. There was no control group. All groups exhibited motor coordination below the average according to a norm-referenced German motor coordination test. A majority of the included children attended special schools, but unfortunately no information on the level of intelligence quotient (IQ) in the sample was given. In the second clinical study (Vance et al., 2006), 99 outpatient children aged 6–12 years were assigned to three diagnostic groups of attention deficit/hyperactivity disorder combined type (ADHD-C), dysthymic disorder, and AnxD, based on a semistructured diagnostic interview. In addition, the researchers included a control group of 20 healthy children in the same age group. All children attended ordinary primary schools and exhibited IQ scores above 70. The participants went through a standardized assessment of neurological subtle signs. The authors found children with AnxDs exhibited more neurological subtle signs, particularly mirror movements, than controls, but fewer than children with ADHD-C.

There is an extensive literature demonstrating an increased prevalence of motor impairment in children with ADHD (Gillberg and Kadesjö, 2003; Pitcher et al., 2003; Fliers et al., 2008), and there is a high degree of comorbidity between AnxDs and ADHD (Costello et al., 2005; Schatz and Rostain, 2006). It would therefore be important to include children with ADHD in studies of motor impairment in children with AnxDs, to ensure motor impairment is not attributable to comorbid ADHD.

The aforementioned review (Emck et al., 2009) also included a smaller clinical study because of the relevance of the findings and the scarcity of studies on this topic. This study found that children with AnxDs had more balance problems than controls (Erez et al., 2004). However, this finding is difficult to interpret, given the fact that 13 of the 20 children with

AnxDs included in the study had a comorbid diagnosis of attention deficit/hyperactivity disorder (ADHD), which may represent a bias given the relationship between ADHD and motor impairment. This study of balance problems in children with AnxDs is, together with a review of the co-occurrence of anxiety and balance dysfunction in adults, regularly interpreted as indicating a specific association between balance problems and anxiety (Balaban and Jacob, 2001; Erez et al., 2004) . However, caution is needed because these assumptions rely on the presence of balance problems, not the absence of other motor problems. To conclude that there is a specific association, it would need to be demonstrated that anxiety is related more to balance problems than to other motor problems.

The association between motor impairment and internalizing problems/AnxDs has also been demonstrated in samples of children with developmental coordination disorder (DCD) (Schoemaker and Kalverboer, 1994; Skinner and Piek, 2001; Pratt and Hill, 2011) and in community samples (Dewey et al., 2002; Kristensen and Torgersen, 2008; Ekornås et al., 2010). Furthermore, there are studies suggesting that motor coordination problems are predictive of the later development of AnxDs (Shaffer et al., 1985; Sigurdsson et al., 2002; Piek et al., 2010). According to a recent twin study, the co-occurrence of clumsiness and anxiety is explained by shared genetic factors rather than direct causal effect (Moruzzi et al., 2010). However, this is partly contrasted by another twin study finding that symptoms of generalized anxiety and separation anxiety in children with motor disorders were due to nonshared environmental effects, suggesting that motor disorder has a causal effect (Pearsall-Jones et al., 2011).

Children with impaired motor abilities have been shown to withdraw from interaction with other children both in the school playground and in kindergarten (Smyth and Anderson, 2000; Bar-Haim and Bart, 2006). Avoidance of feared situations is a key feature of AnxDs (American Psychiatric Association, 2000). Impaired motor abilities may make it even more difficult for an anxious child to confront an anxiety-provoking situation, such as not having his or her parent around (characteristic of separation anxiety disorder), or risking the critical appraisal of others (characteristic of social phobia). Confronting and enduring anxiety-provoking situations are important elements of exposure-based cognitive behavioral therapy, which is the psychotherapy with the best empirical support in the treatment of AnxDs in children and adolescents (Compton et al., 2004). It is reasonable to assume that if a child has substantial motor coordination problems, this will affect how much anxiety the exposure tasks induce, in addition to affecting the child's ability to execute the task. Knowledge about the frequency and degree of motor impairment among children with anxiety disorders referred to

mental health services is potentially important when evaluating the need for adjustment of standardized treatment programs. Acknowledging each child's individual motor ability is also important to give parents and teachers the opportunity to modify the demands of everyday life to a level the child is able to handle.

To the best of our knowledge, there are no clinical studies on the relationship between AnxDs and motor impairment that assess motor impairment with a standardized motor performance test in children who have been thoroughly diagnosed. To address this paucity of research, the present study aimed to examine and compare the frequency and degree of motor impairment among children with AnxDs, children with ADHD, and children with comorbid AnxD and ADHD referred to general child and adolescent psychiatric outpatient clinics, and among nonreferred children from adjacent schools. Furthermore, we wanted to explore whether motor profiles varied between the clinical groups.

2. Methods

2.1. Participants

A total of 141 children aged 7–13 years participated in this study, including 41 children with AnxDs, 39 children with ADHD, 25 children with comorbid AnxD and ADHD, and 36 controls. The clinical sample included referrals to two Norwegian municipality outpatient child and adolescent psychiatric clinics over a 17-month period (September 2007 to February 2009). The parents of consecutively referred children between 7 and 13 years (n = 421) were interviewed using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (6–18 years): Present and Lifetime Version (Kiddie-SADS P/L) (Kaufman et al., 1997). Participants were recruited from children who met DSM-IV (American Psychiatric Association, 2000) criteria for AnxD and/or ADHD, and who did not meet the exclusion criteria. Those that consented to participate (n = 105) and those that declined participation (n = 82) did not differ in mean age, mean score on the Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983), or gender distribution. Controls were recruited from nonreferred children from neighboring schools. All except three children were Caucasian. Eighty-four children were excluded because of the presence of the following exclusion criteria: Biological mother not available (e.g., child adopted; n = 16); mother did not speak sufficient Norwegian to fill in the questionnaires (n = 19); child met DSM-IV criteria for Asperger's syndrome (n = 12); child had an IQ below 70 (n = 9); child was on medication for

ADHD (n = 16); child had a known neurological disease (n =4); or child had ADHD and a history of AnxD or subthreshold AnxD, but did not meet DSM-IV criteria for a current AnxD (n = 8). This last exclusion criterion was selected to ensure that the "pure" ADHD group did not include children with subthreshold anxiety. Sample characteristics are presented in Table 1, and a more thorough description of the recruitment and diagnostic procedures is presented in a previous article (Skirbekk et al., 2011). Reports regarding sleep and attention, using data from the current sample, have recently been published (Hansen et al., 2011; Skirbekk et al., 2011).

2.2. Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics and by the Norwegian Social Science Data Services. Participation depended on written informed consent from parents. If parents consented to participate in the study, written informed consent was obtained from children 12 years or older and verbal informed consent from children younger than 12 years.

2.3. Measures

2.3.1. Diagnoses

DSM-IV-based diagnoses were obtained by interviewing the mothers using the Kiddie-SADS P/L (Kaufman et al., 1997). We used the revised version, which includes the assessment of pervasive developmental disorders. All interviews were administered by authors 1, 2, and 5, who are all experienced clinicians. Interrater reliability was assessed by rescoring audiotapes from 39 random interviews. This resulted in kappa = 0.90 for ADHD and kappa = 0.88 for any AnxD. After the interview the interviewer scored the CGAS (Shaffer et al., 1983), as an assessment of the child's overall severity of disturbance.

2.3.2. Intelligence

The IQ was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). The WASI provides a brief assessment of IQ and has recently shown a high internal and external validity (Canivez et al., 2009).

2.3.3. Motor impairment

Motor impairment was assessed using the Movement Assessment Battery for Children (M-ABC) (Henderson and Sugden, 1992). The M-ABC is one of the few motor assessment batteries available in a Nordic language and is well known in Norwegian clinics. The M-ABC is divided into four age bands from 4 to 12 years of age (the three age bands from 7 to 12 years were used in this study). Each age band covers the same types of skills and assesses motor impairment in three areas: manual dexterity (three tasks), ball skills (two tasks), and static and dynamic balance (three tasks). Raw scores on each item are converted to age-normed scores, ranging from 0 to 5. Normed scores are summed to form three subscale scores and a total score. The total score ranges from 0 to 40, where higher scores represent greater impairment. In the present study, children aged 13 years were evaluated with the norms for 12 year old children. The M-ABC is widely used and recommended in the assessment of motor impairment in children both in research and clinical practice (Geuze et al., 2001), and has shown moderate to good interrater and test-retest reliability (Smits-Engelsman et al., 2008).

2.4. Statistical analysis

Differences between the groups (i.e., AnxDs vs ADHD vs comorbid AnxD + ADHD vs controls) regarding M-ABC total score and subscale scores were analyzed using analysis of covariance (ANCOVA), adjusted for differences in IQ and gender distribution. The residuals of the analysis were scrutinized and found to exhibit a distribution that was sufficiently close to normal to allow the ANCOVA. The significance level for conducting post hoc analyses was set to 0.05. Exact chi-square test was used to compare each of the clinical groups with the control group, on the proportion of children scoring at or below the 5^{th} percentile on the M-ABC. All post hoc *P*-values were corrected using the Holm adjustment for multiple analyses (Aickin and Gensler, 1996). There were no missing data for any of the children. All *P* values presented are two-tailed. Statistical analyses were performed using the Statistical Package for Social Sciences, version 15.0 for Windows (SPSS Inc, 2006) and R (R Development Core Team, 2010).

3. Results

The mean and standard deviations of the M-ABC scores are presented in Table 1. The analyses of differences between the groups (i.e., AnxD vs ADHD vs comorbid AnxD + ADHD vs nonreferred controls) regarding M-ABC scores, adjusted for IQ and gender, are presented in Table 2. On the M-ABC total score, the AnxD group was significantly more impaired than the controls ($P = 0.004$). The ADHD group ($P = 0.052$), and the comorbid AnxD + ADHD group ($P = 0.052$) exhibited a non-significant tendency towards being more impaired than controls. There were no significant differences between clinical groups ($P \geq 0.926$). Similarly, the AnxD group was significantly more impaired than controls on the M-ABC manual dexterity subscore ($P = 0.013$). The ADHD group ($P = 0.168$), and the comorbid AnxD + ADHD group ($P = 0.079$) were not significantly more impaired than controls. There were no significant differences between clinical groups ($P \geq 0.742$). There were no significant post hoc group comparisons on the M-ABC ball skills subscores ($P \geq 0.422$). The ANCOVA value was not significant beyond the 0.05 level for the differences in M-ABC balance subscores. To explore whether the motor impairment among children with AnxDs was mainly attributable to social phobia or obsessive/compulsive disorder (OCD), the analyses were repeated with these children excluded. This did not change the results significantly.
The number of children scoring above or below the 5th percentile on the M-ABC in each group is presented in Table 3. The chi-square test for the whole table was significant (χ^2 (3) = 16.60, $P = 0.001$). Post hoc chi-square tests applied to evaluate whether there was a significant difference between the proportion in each of the clinical groups compared with the control group scoring at or below the 5th percentile of the M-ABC total score, were significant for all three clinical groups (AnxD vs control, $P < 0.001$; ADHD vs control, $P = 0.026$; comorbid AnxD + ADHD, $P = 0.010$). To explore the level of motor impairment in the control group, we calculated the median M-ABC total score in this group, median = 4.75. According to the M-ABC manual a median of 4.75 is between the 49th (M-ABC total score = 4.5) and the 45th (M-ABC total score = 5.0) percentile.

4. Discussion

In the present study, we investigated motor impairment in referred children aged 7–13 years with AnxDs, compared with children with ADHD, children with comorbid AnxD and

ADHD, and nonreferred controls without AnxD and ADHD. Our main findings were that children with AnxD exhibited significantly higher scores on motor impairment on the M-ABC compared with controls, after adjusting for differences in IQ and gender distribution. There were no significant differences between the clinical groups. Children with AnxDs exhibited the same profile of motor impairment as other clinical groups. A substantial proportion (46%) of children with AnxDs scored below the 5th percentile on the M-ABC.

4.1. Motor impairment

The findings of greater motor problems in children with AnxDs than in controls and the lack of group differences in motor problems between children with AnxDs and children with ADHD in the present study are in line with the findings in population-based studies (Kristensen and Torgersen, 2008; Ekornås et al., 2010). However, establishing that there is a significant difference in motor impairment scores does not automatically imply motor impairment is an important problem among children with AnxDs. Motor impairment may occur with varying degrees of severity, from slight clumsiness to DCD. The main DSM-IV criterion for DCD is: "Performance in daily activities that require motor coordination is substantially below that expected given the person's chronological age and measured intelligence" (American Psychiatric Association, 2000). The clinical diagnosis requires both a test score of motor performance below the 15th percentile and information about poorer motor performance in the child's daily life activities. We did not have information about daily life activities in the current study, and accordingly we were not able to diagnose DCD. However, according to a recent study, motor coordination below the 5th percentile represents a challenge in a multitude of daily activities both at home and at school (Wang et al., 2009). Hence, it is reasonable to assume that an M-ABC score below the 5th percentile, among children with IQ above 70, represents a potential problem for the child. In the present study, we found 19 (46%) of the 41 children with AnxD without comorbid ADHD to exhibit motor coordination below the 5th percentile. This is in line with a recent study that found 12 (44%) out of 27 children with AnxDs in a community sample had motor problems, as defined by M-ABC scores below the 5th percentile (Ekornås et al., 2010). These findings indicate that substantial motor problems are frequent in children with AnxDs. However, motor impairment is not among the co-occurring conditions considered important in recent recommendations on the assessment and treatment of AnxDs in children (Connolly and Bernstein, 2007). Hence, an

evaluation of motor ability is generally not included in the assessment of referred children with AnxDs.

The causal direction, if any, between anxiety and motor impairment is not established and there are conflicting results. Unfortunately the cross-sectional design of the current study does not allow us to analyze the causal relationship. To our knowledge, there are no longitudinal studies suggesting that anxiety may lead to motor impairment. However, there are a few studies indicating that motor impairment precedes anxiety (Piek et al., 2010; Pearsall-Jones et al., 2011), but it has also been suggested that the relationship between anxiety and motor impairment is explained by shared genetic factors rather than direct causal effect (Moruzzi et al., 2010). More research is needed both to establish whether there is a causal relationship between AnxDs and motor impairment, the direction of this causality, and finally whether the co-occurrence of AnxD and motor impairment affects the course of the individual disorders.

4.2. Motor profiles

An additional aim of our study was to explore the motor profiles in the four groups. The three clinical groups exhibited approximately the same pattern of the three subscale scores (Table 2), suggesting that there are no fundamental differences in the patterns of motor impairment between the clinical groups. Some studies emphasize the finding of balance problems in connection with anxiety, both in children (Erez et al., 2004) and in adults (Balaban and Jacob, 2001), and suggest this finding implies a specific link between balance and anxiety. The lack of group differences on balance tests in our study may very well be due to the use of different balance tasks than those used in the aforementioned studies. However, the similarity of profiles between the clinical groups in our study, together with the fact that the AnxD group exhibited significantly higher manual dexterity impairment scores compared to controls, do not support the assumption of a specific link between balance and anxiety. The suggestion that anxiety and balance are uniquely linked would need the demonstration of more balance problems than other motor problems in subjects with anxiety, and more balance problems among subjects with anxiety than among subjects with other psychiatric conditions known to be related to motor problems (e.g., ADHD).

4.3. Limitations

The motor assessment of the participants was performed by the authors. Because the authors had also conducted the Kiddie-SADS interviews, for practical reasons we were not always blind to the diagnostic information obtained in the interviews. Furthermore, the study was performed using a clinical sample of limited size (41 children with AnxD, 39 children with ADHD, 25 children with comorbid AnxD + ADHD, and 36 controls). Given the established relationship between ADHD and motor impairment in the literature, and the differences in the estimated means of M-ABC total score between the ADHD groups and controls, the reason these differences are shy of significance may be that the sample size is not large enough to withstand adjustment for IQ and gender in addition to post hoc correction for comparing four different groups. The fact that the M-ABC consists of different tests for different age-ranges may also be considered a limitation. Furthermore, none of the available motor tests covers the full range of motor abilities and the use of only one test may lead to an underestimation of motor problems. In addition, the lack of information about daily activities from interviews or questionnaires in the current study may have lead to an overestimation of motor problems, by assuming motor problems in children with test performance below the 5th percentile, but also to underestimation, by not recognizing motor problems in children with motor performance in the borderline area between the 5th and the 15th percentile. For practical reasons, the Kiddie-SADS P/L interview was only administered to parents and not to children. Although there is reason to expect that the parents of referred children in this age group are aware of internalizing and externalizing problems that lead to impairment, the establishment of a diagnosis based on a single informant is not regarded as best practice. There is a general problem of comorbidity in clinical populations. We have, to some extent, controlled for this by creating separate diagnostic groups, but there is always the possibility of other comorbid factors affecting motor ability (e.g., dyslexia). Finally, our control group was a convenience sample of nonreferred children from nearby schools. Because they were not drawn randomly, the children in the control group might not be fully representative of the population of nonreferred children. However, the finding that 5.6% of the control group score below the 5th percentile together with the finding that the median of the control group was between the 49th and 45th percentile according to the M-ABC norm group, suggest that the control group in the present study did not exhibit better motor function than the M-ABC norm group.

4.4. Clinical implications

Notwithstanding the aforementioned limitations, the present results add to the understanding of the developmental challenges many children with AnxDs face, by indicating that motor impairment is a frequent and significant problem among children with AnxDs. Motor proficiency is important in the typically developing child. Accordingly, motor impairment may hamper a child's development of independent mastery and restrict the child's opportunities for social interaction. Considering the notable proportion of children with AnxDs who exhibit substantial motor impairment, both in the present study and in population-based studies, assessment of motor ability in children with AnxDs should be routinely conducted. Knowledge of the child's motor ability is important to modify the demands of both everyday life and treatment programs to a level the child is able to handle.

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Table 1 Sample characteristics.

Group	AnxD	ADHD	AnxD + ADHD	Nonreferred controls
n	41	39	25	36
Boys/Girls	27/14	30/9	12/13	21/15
Age, mean (*SD*)	10.9 (2.0)	9.8 (1.6)	10.1 (1.9)	10.7 (2.3)
IQ, mean (*SD*)	97.2 (12.5)	100.6 (15.6)	96.3 (11.6)	109.4 (12.5)
ADHD/I, *n*	–	17	12	_
ADHD/C, *n*	_	21	11	_
ADHD/H, *n*	_	1	2	_
Separation anxiety, *n*	15	_	12	_
Specific phobia, *n*	10	_	10	_
Social phobia, *n*	16	_	3	_
Generalized anxiety disorder, *n*	6	_	2	_
Panic disorder, *n*	2	_	_	_
Agoraphobia, *n*	2	_	1	_
Obsessive/Compulsive disorder, *n*	10	_	4	_
M-ABC totalscore, mean (*SD*)	11.7 (6.5)	10.0 (6.2)	11.0 (6.8)	5.4 (4.2)
M-ABC manual dexterity, mean (*SD*)	6.7 (4.4)	5.6 (3.7)	6.3 (4.7)	2.8 (2.8)
M-ABC ball skills, mean (*SD*)	2.2 (2.1)	2.0 (2.2)	2.0 (2.7)	1.2 (1.8)
M-ABC balance, mean (*SD*)	2.7 (2.6)	2.3 (2.3)	2.7 (2.6)	1.4 (1.8)

AnxD, anxiety disorder; ADHD, attention deficit/hyperactivity disorder; SD, standard deviation; IQ, intelligence quotient; ADHD/I, ADHD/inattentive type; ADHD/C, ADHD/combined type; ADHD/H, ADHD/hyperactive type; M-ABC, Movement Assessment Battery for Children.

Table 2

ANCOVA of M-ABC subscale and total scores, adjusted for IQ and gender.

Variable	AnxD	ADHD	AnxD + ADHD	Controls	*F*	*df*	*P*	Significant post hoc group comparisons[b]
	Predicted mean[a]	Predicted mean	Predicted mean	Predicted mean				
M-ABC								
Manual dexterity	6.96	5.97	5.34	4.12	**7.71**	5, 135	<0.001	AnxD > controls
Ball skills	1.81	1.79	1.48	0.87	**2.49**	5, 135	0.034	
Balance	2.63	2.29	2.53	1.49	1.74	5, 135	0.130	
Total score	11.39	10.05	10.63	6.48	**6.67**	5, 135	<0.001	AnxD > controls

Significant *F* values in bold; M-ABC, Movement Assessment Battery for Children; AnxD, anxiety disorder; ADHD, attention deficit/hyperactivity disorder; *SD*, standard deviation. [a]Predicted mean represents an estimated mean for boys with IQ = 100. [b]Holm corrected.

Table 3

Cross-tabulation of M-ABC total scores above and below 5th percentile, and group.

	AnxD	ADHD	AnxD + ADHD	Controls	Total
M-ABC > 5th percentile, *n (%)*	22 (53.7)	29 (74.4)	16 (64.0)	34 (94.4)	101 (71.6)
M-ABC ≤ 5th percentile, *n (%)*	19 (46.3)	10 (25.6)	9 (36.0)	2 (5.6)	40 (28.4)
Total, *n*	41	39	25	36	141

M-ABC, Movement Assessment Battery for Children; AnxD, anxiety disorder; ADHD, attention deficit/hyperactivity disorder.

II

III